A STUDY OF COGNITIVE EVOKED POTENTIAL AND ARTERIAL OXYGEN SATURATION IN STABLE COPD PATIENTS

Dissertation submitted

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the award of the degree of

M.D.PHYSIOLOGY

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APRIL 2015

BONAFIDE CERTIFICATE

This is to certify that the dissertation titled **"A STUDY OF COGNITIVE EVOKED POTENTIAL AND ARTERIAL OXYGEN SATURATION IN STABLE COPD PATIENTS''** is a bonafide record work done by **Dr. Rowena Victor,** under my direct supervision and guidance, submitted to The Tamil Nadu Dr. M. G. R. Medical University in partial fulfillment of University regulation for **M.D., Branch-V (Physiology).**

Dr.AL.Meenakshi Sundram,M.D., D.A.,
Dean
Govt. Stanley Medical College
Chennai – 600 001.

Dr.K.Balasubramanian,M.D.,
Professor and HOD
Govt. Stanley Medical College
Chennai - 600001

DECLARATION

I, **Dr. Rowena Victor,** solemnly declare that the dissertation titled ‘‘**A STUDY OF COGNITIVE EVOKED POTENTIAL AND ARTERIAL OXYGEN SATURATION IN STABLE COPD PATIENTS’’** has been prepared by me. I also declare that this work was not submitted by me or any other, for any award, degree, diploma to any other University board either in India or abroad. This is submitted to The Tamil Nadu Dr.M.G.R. Medical University, Chennai in partial fulfillment of the rules and regulation for the award of **M.D degree Branch-V (Physiology)** to be held in **April-2015.**

Place : Chennai **Dr. ROWENA VICTOR**

Date :

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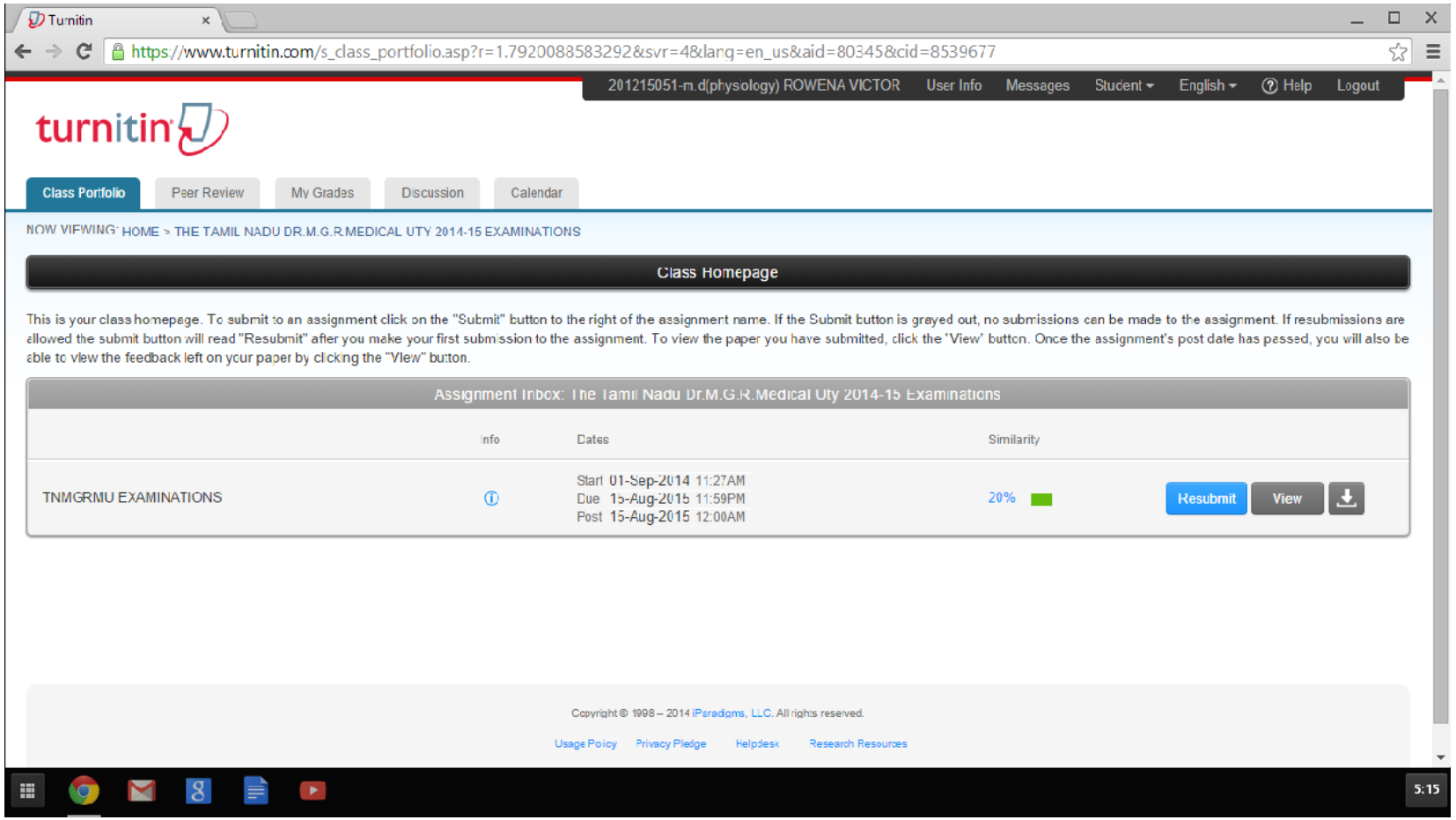
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Title of Work	*A study of Cognitive Evoked Potential and Arterial Oxygen Saturation in Stable Chronic Obstructive Pulmonary Disease Patients.*
Principle Investigator	: Dr.Rowena Victor
Designation	: II Year Postgraduate
Department	: Physiology
Guide	: Dr.K.Balasubramanian,M.D, Prof & HOD, Dept.of Physiology, Govt. Stanley Medical College ,Chennai – 1.

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ABBREVIATIONS

COPD	CHRONIC OBSTRUCTIVE PULMONARY DISEASE
GOLD	GLOBAL initiative for OBSTRUCTIVE LUNG DISEASE
ABG	ARTERIAL BLOOD GAS analysis
FEV	FORCED EXPIRATORY VOLUME
FEV_1	FORCED EXPIRATORY VOLUME in 1sec
FVC	FORCED VITAL CAPACITY
MMSE	MINI MENTAL STATUS EXAMINATION
P_{300}	POSITIVE wave in 300 ms
SaO_2	ARTERIAL OXYGEN SATURATION
Pa O_2	PARTIAL PRESSURE OF OXYGEN
EP	EVOKED POTENTIAL
N_{100}	NEGATIVE WAVE IN 100ms
PFT	PULMONARY FUNCTION TEST
EEP	EVENT EVOKED POTENTIAL
CEP	COGNITIVE EVOKED POTENTIAL
BMR	BASAL METABOLIC RATE
Ag/Ag Cl	SILVER / SILVER CHLORIDE
SPSS	STATISTICAL PACKAGE FOR SOCIAL SCIENCES
ANOVA	ANALYSIS OF VARIANCE
m sec	MILLISECONDS
Kg/m^2	KILOGRAM/METER^2

ABSTRACT

A STUDY OF COGNITIVE EVOKED POTENTIAL AND ARTERIAL OXYGEN SATURATION IN STABLE COPD PATIENTS

DEGREE FOR WHICH SUBMITTED : DOCTOR OF MEDICINE (MD) IN PHYSIOLOGY

SUPERVISOR AND GUIDE : PROF.DR. K.BALASUBRAMANIAN.M.D. HEAD OF THE DEPARTMENT

DEPARTMENT : DEPARTMENT OF PHYSIOLOGY

COLLEGE : GOVT.STANLEY MEDICAL COLLEGE. CHENNAI – 600 001

UNIVERSITY : THE TAMILNADU DR. M.G.R. MEDICAL UNIVERSITY, CHENNAI – 600 032

YEAR : 2012-15

BACKGROUND:

Chronic obstructive pulmonary disease (COPD) is a complex multicomponent disease which is associated with cognitive impairment due to neuronal damage mediated by hypoxia. Cognitive impairment affects the self-management, clinical management and pulmonary rehabilitation of COPD subjects. Progressive impairment of the auditory P_{300} evoked potential with prolonged latency occurs with increasing severity of COPD. So routine screening of COPD patients for cognition is helpful in assessing the progression of the disease.

AIM:

To assess the cognitive function and to correlate it with arterial oxygen saturation in stable COPD patients and age matched controls.

OBJECTIVE:

To assess cognitive functions in stable COPD patients and age-matched healthy controls using Cognitive evoked potential (CEP) study, Mini mental status examination (MMSE) and Stroop test to correlate them with Arterial oxygen saturation (SpO_2) using Pulse oximetry and Arterial oxygen tension (PaO_2) by arterial blood gas analysis.

MATERIALS AND METHODS:

The study population were 50 Stable COPD patients and 50 controls. They were subjected to MMSE, Stroop test, and CEP study and SpO_2 measured by Pulse oximetry. In addition, Arterial blood gas analysis was done for the patients to measure PaO_2. The data were analyzed using Mean, Standard deviation, Independent t-test, ANOVA and Tukey post hoc test and pearson's correlation were used for analysis. The mean difference was significant when $p < 0.05$ level.

RESULTS:

In stable COPD patients, MMSE score was significantly lower, interference score was significantly increased in Stroop test and prolonged N_{100},P_{300} latency and reduced P_{300} amplitude in CEP study than in controls. SpO_2 by pulse oximetry shows significant decrease in patients than in the controls. There is positive correlation between P_{300} amplitude and PaO_2 in the patients.

CONCLUSION:

There is significant cognitive impairment in Stable COPD patients as evidenced by MMSE, Stroop test, and CEP study We recommend CEP study as a screening tool in

Stable COPD patients to detect early cognitive impairment so that timely intervention can be planned to improve the quality of their life.

Key words : Stable COPD patients, Cognitive evoked potential, P_{300}, MMSE, Stroop test, Cognition.

INTRODUCTION

The Objective of Global initiative for chronic Obstructive Lung Disease (GOLD) is," to increase awareness of COPD among health related officials and general community, to improve the diagnosis, management and prevention of COPD, and to encourage exploration in COPD".

COPD is a major public health problem. It is a group of chronic lung disorders, specifically encompassing Emphysema and Chronic Bronchitis and about 600 million people are affected globally and it is now the fourth leading cause of death and it is the only cause of mortality whose incidence continues to rise and will be the third cause by 2020[1]. In India, 53% of all deaths were estimated to be due to Non communicable diseases and 44% of DALY (disability adjusted life years) lost in 2005.Of these7% deaths and 3% DALYs lost were due to Chronic Respiratory diseases [2]**.**There are 30 million COPD patients in India as estimated approximately[3]**.** In India burden of Chronic Bronchitis was estimated as 14.84 million.

The reported prevalence is from 2 to 22% in men & from 1.2 to 19% in women**.**[4] Tobacco use is the main cause of global wave of smoking-related illnesses resulting in 5.4 million deaths worldwide each year and it will increase to 6 million by 2015. 30% of the tobacco-related deaths will be caused by chronic respiratory diseases[5]. Cigarette smoking is the leading cause of COPD which causes 56 times more possibility of illness than the non-smokers[6].

Passive smoking, air pollution, and occupational chemical fumes or dust may act synergistically with active smoking to increase the risk of COPD[7].

COPD is a multicomponent non communicable disease with not only primary pulmonary involvement but co morbidities like cardiovascular disease, osteoporosis, anaemia depression and cognitive impairment is one among them. The Airflow limitation in COPD is not reversible and the disease is progressive but it is preventable and treatable[8.] It is a multisystem disorder with both physical effects and impaired psychological and cognitive functioning. In addition to the involvement of motor nerve, encephalopathy and cognitive dysfunction have been noted in patients with chronic respiratory insufficiency. Kayakan et al (2001) observed that cigarette smoking, limitation of airflow, and COPD in the last stage causes hypoxemia and hypercapnia which involves the pontomedullary portion of the brain[9.] Stable COPD patients are those who are on regular medical intervention for the past 4 weeks.

Cognitive impairment is one of the extra pulmonary feature of COPD[10] Cognition is the higher intellectual function of the brain. The cognitive decline of the individual results in a great burden on the self, family and community. The incidence of cognitive dysfunction in COPD patients varies in different studies from 12% to 88%[11]. Domains of cognition are memory, learning ability both visual and verbal, attention or vigilance, concentration, abstract thinking, and problem solving. Neurocognitive defects such as slowed information processing speed, poor learning, poor memory and attention deficit are well documented in COPD patients by various studies. The most affected cognitive

domain is memory and attention, though speed, coordination and learning abilities are also affected. Increasing age and low level of education are also associated with cognitive impairment. J. W. Dodd et al in 2010 described a specific pattern of cognitive impairment in patients with COPD.[12] Patients find very difficult to breath, and are much depressed, dysfunctional, disabled, desperate, and are very difficult to deal with. They are encouraged to become more knowledgeable about the disease, to actively involve in self management and to become more independent in daily activities[2]. Cognitive dysfunction reduces the level of functioning[13,14,] and it is associated with poor compliance with both medication and oxygen therapy which increases the risk of acute exacerbation.

Cognitive impairment affects functional, social, emotional, affective, and communication skills. Also Impairment of Cognition predicts mortality in hypoxemic COPD patients.[15] A good cognitive status is essential for the individual to understand his real state and to abstain from smoking, which makes his life dejected by affecting his lung function. Level of cognitive functioning of these patients must be taken into consideration before self-care can be planned and it is modified toward the patient's individual capability and needs. Number of studies have been done in the past which says that patients with COPD have poor quality of life and is again confirmed by Kaplan and Ries[16,17].

In most of the previous studies, they had used neuropsychological battery of tests to assess various domains of cognition. There are only few studies in the

literature which have employed electrophysiological tests to quantify cognitive impairment in COPD. Also Pulmonary Rehabilitation which is an important aspect of treatment for COPD patients should include initial evaluation of patient's cognition, psychological state, social support etc which is very important to improve the quality of life in COPD patients. Also cognitive training should be included in the treatment schedule of COPD patients especially in long term Pulmonary rehabilitation programs.

The term arterial oxygen saturation the percentage of Hb molecules which are saturated with oxygen (SpO_2) which is SaO_2 measured by pulse oximetry.SpO_2 is related to partial pressure of oxygen in a complex way in oxyhaemoglobin dissociation curve. Partial pressure of oxygen is the arterial oxygen tension and it is blood oxygen level Hypoxemia produces varying responses in different tissues greatest need is to the brain and heart.

In the present study, in addition to the Mini Mental State Examination(MMSE) and Stroop test, Cognitive evoked potential study was done to assess cognitive function in the Stable COPD patients. MMSE is a brief, quick objective method of assessing global cognitive functioning. It is a reliable and validated method commonly used to assess cognitive status. The Stroop Colour Word Test is used to assess cognitive flexibility.[18] The interference score in Stroop test gives the measure of inhibition of a habitual response (reading) which is part of the executive functioning. It measures focussed attention. CEP analysis is to investigate specific types of information processing by the brain. Cognitive evoked potentials are electric signals from the brain generated while

performing various cognitive tasks. It is produced when the person attends to and discriminates between stimuli which differ from one another in some dimension such as modality, intensity, frequency or duration. Cognitive evoked potential study is recommended for detecting and quantifying early cognitive impairment which is not usually detected by other traditional methods of assessment of cognition.[19]

The present study was undertaken to assess the cognition in the Stable COPD patients using Mini Mental State Examination and Stroop test and Cognitive Evoked Potential study and compare it with that of normal individuals, and to correlate with Arterial partial pressure of oxygen.

The possibility of using cognitive evoked potential as an investigatory tool to detect early cognitive impairment in Stable COPD patients was being explored in the present study along with neuropsychological tests.

I hypothesise that stable COPD patients have cognitive dysfunction depending upon the severity of air flow obstruction due to chronic hypoxia.

Review of literature

REVIEW OF LITERATURE

Chronic obstructive pulmonary disease (COPD) is a multi component disease in which cognitive dysfunction is one of the components. Cognitive function is essential for daily activities like attention, concentration, memory, logical thinking, reasoning and execution of a motor act.

In this section, the literature relevant to COPD and COGNITION in terms of the following side headings is being discussed.

1. Historical Aspects
2. COPD
3. Pulmonary Function Tests
4. Cognition
5. Neuropsychological test – MMSE and Stroop test
6. Neurophysiological test – Cognitive evoked potential study
7. Pulse Oximetry and Arterial Blood Gas Analysis.

HISTORICAL ASPECTS

In the early days, the term lung was not mentioned in the body except for "pneuma" or vital spirits and air of universe. Respiratory system was studied after circulatory system and this was done by **Robert Boyle** (1627-1691), an Irish scholar. He proved that candle will stop burning when kept in an airless jar. **Joseph Priestly** discovered oxygen, dephlogisticated air. **Antonie Lavoisier,** (1743-1794) a French chemist, confirmed that oxygen is in inspired air and carbon dioxide is in expired air.[24]

People regarded life as one and the same with breathing and life starts and finishes with breathing. The **BIBLE say**s that God breathed the breath of life into the nostrils of **ADAM** and then took a rib from ADAM'S chest, to give life to **Eve.** In 5th and 6th B.C., **Hippocrates** said that the function of lung is to cool the heart. In 18th Century, the true role of breathing was established after the study of chemistry of gases.[25]

The word Emphysema has its origin from the Greek meaning "to blow into" and was described by **Bonet** in 1676 and **Morgagni** in 1769. **Ruysh** in 1721, described emphysema in humans with illustrations.

Matthew Baillie in 1807, documented, illustrated and denoted the real destructive character of emphysema.

In 1892, **William Osler** in his "Text book of Medicine" described hypertrophic emphysema as," a well marked clinical affection, with enlargement of lungs due to distension of airways and atrophy of their walls, and clinically by imperfect aeration of blood and more or less dyspnoea."[26]

J. Gough in 1952, described centrilobar emphysema. **Gough & Wentworth** developed paper section technique.

McLean gave a comprehensive microscopic description of emphysema and demonstrated the relationship of destruction to inflammatory alterations of the bronchioles and vessels.

Laennec, who invented stethoscope in 1819 first characterised emphysema by making clear-cut peculiarities of interstitial emphysema and emphysema proper and correlated the enlarged airspaces to the clinical syndrome of emphysema. He documented that air trapping and increased collateral ventilation were features of emphysema and the primary site of obstruction were the peripheral airways. Airspace enlarges as age increases, but it was distinguished from emphysema. He was the first to describe an association of emphysema with chronic bronchitis and described the pathology of bronchiectasis.[27]

Galen(129-200 AD) did a volumetric experiment on human ventilation. In **1793, Menezies R** determined the tidal volume using body plethysmograph. **John Hutchinson,** a surgeon pointed out that the volume of air exhaled after a full inflation is an indicator of longevity of life. The water-sealed volume-displacement spirometer was invented by him in 1844 to measure the vital capacity i.e. the capacity to live. Spirometry is the most simple and useful method available to evaluate the pulmonary function.

Early work on respiratory function was done in 1920s with blood gas

measurements technique. In 1925, **Meakins & Davies** explained most derangements of function in terms of disorders of blood gases**. Barcroft & Haldane** clarified the basic gas transport.[28]The electrolyte theory of dissociation was proposed by **Svante Arrhenius NP** (1859-1927) for which he was awarded Nobel prize. The definition for acid was given by **Johannes N Bronsted (**1879-1947). The relationship between pH, pKa, concentration of acid and conjugate base is expressed by the Henderson-Hasselbach equation given by **Lawrence J Henderson** (1878-1972) and **KA Hasselbalch** (1874-1962)[29].

The name P_{300} was given by **Smith et al**. It is a parietocentral positivity that occurs when a subject detects an informative task-relevant stimulus. It is obtained 300ms after a subject makes a simple sensory discrimination. P_3 or P_{300} is the third major positive peak in the late sensory evoked potential (Ritter et al., 1968) and the late positive component (**Sutton e**t al., 1965, 1967). Sutton et al described this late positive component and it is endogenous**. Ritter and Vaughan** in 1969 used the "**oddball paradigm**" wherein the subject detects occasional target signals randomly interspersed among frequent standard stimuli. He also described parietocentral scalp distribution of the P_{300}. Previous research on P_{300} has been done exclusively in humans. But localisation of the neural generators contributing to P_{300} will require depth recording and lesion experiments which were done in **cats** which gives anatomical and physiological information.

Aristotle gave attention to the cognitive process more than twenty-three centuries ago. Aristotle focussed on cognitive areas pertaining to memory,

perception, and mental imagery. In the15th century, it meant thinking and awareness. Other scientists like **Wilhelm Wundt, Herman Ebbinghaus, Mary Whiton Calkins, and William James,** and some others offered their contributions to the study of cognition.

CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Natural History of COPD:

In the year 2009, the Framingham Offspring cohort study (prospective) was done from adolescent to old age for 23years in both sexes. The following observations were made:

(1) the normal rate of decline in lung function in healthy non-smokers is less

(2) the dreadful effect of smoking cigarettes on the rate of lung function decline is similar in both sexes

(3) the presence of respiratory symptoms identifies that smokers are particularly susceptible to the development of airflow limitation.

(4) the advantage of quitting smoking is more marked when it is done earlier.

In the Rotterdam Study, that addresses the important issue of markedly high incidence of COPD in the youngest women, which suggests a further shift toward females in the sex distribution of COPD. Despite this

potential change in incidence, mortality remains higher in males than females, even in well-matched BODE [body mass index, airway obstruction, dyspnea, and exercise capacity] patients.

Chronic obstructive pulmonary disease (COPD) is defined as a disease state characterized by airflow limitation that is not fully reversible accompanied by inflammatory responses to noxious particles or gases. COPD includes emphysema, chronic bronchitis, and small airways disease. COPD is present only if chronic airflow obstruction occurs. It excludes asthma, bronchiectasis, bronchiolitis, and cystic fibrosis. It causes maximal expiratory airflow limitation and it is the severity of the limitation that is abnormal in COPD.

Risk factors include host and environmental factors. By 1964, the Advisory Committee to the Surgeon General of the United States had concluded that cigarette smoking was a major risk factor for mortality from chronic bronchitis and emphysema. Second less common risk factor is a hereditary deficiency of α1 antitrypsin.

Lower socioeconomic status is associated with significantly increased risk for development COPD. Men often have a significantly increased risk for development COPD due to cigarette smoking and the habit of retaining the cigar in the mouth between puffs and extinguishing and relighting cigars. Other factors include air pollution, infection especially in childhood, climate, hereditary, socioeconomic status, atopy, nonspecific airway hyper responsiveness, diet and nutrition. Tobacco smoke is a complex mixture of

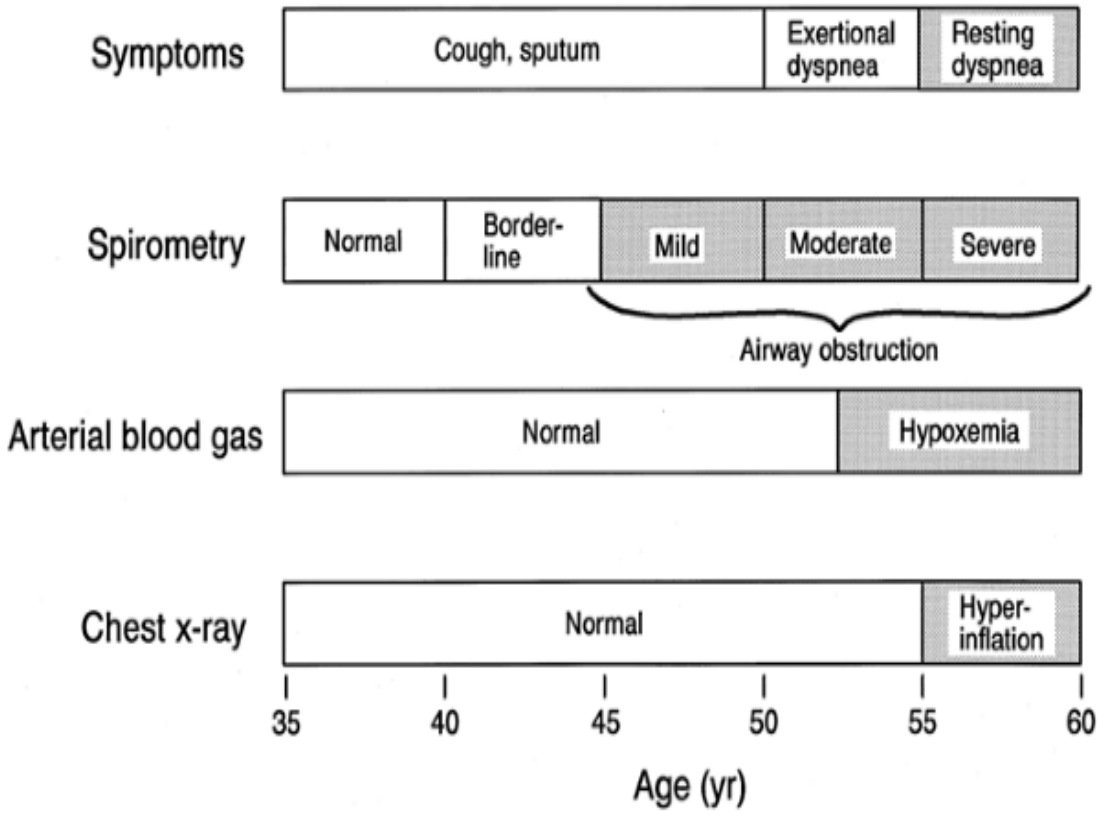
more than 100 volatile and particulate chemical substance. The enormous impact of smoking and COPD on mortality was first studied by **Doll & Hill.**[34]

Individuals whose lung function is impaired for any reason are at increased risk for development of symptomatic COPD and this is called as **Horse race effect**[34]**.**

In the early stages of the disease there are no clinical findings. By the time the disease is diagnosed the disease is far advanced. Subsequent longitudinal studies have shown accelerated decline in the volume of air exhaled within the first second of the forced expiratory manoeuvre (FEV_1) in a dose-response relationship to the intensity of cigarette smoking, which is typically expressed as **pack-years** (average number of packs of cigarettes smoked per day multiplied by the total number of years of smoking). The traditionally higher rate of smoking among males is the likely explanation for the higher prevalence of COPD among males[2]

FIGURE - 1

TYPICAL PROGRESSION OF THE SYMPTOMS OF COPD.



Pathophysiology:

Most important abnormalities that occur in COPD are,

a) Chronic obstruction

b) Entrapment of air in the alveoli and marked destruction of alveolar walls

c) Chronic infection

d) Increased airway resistance and increased work of breathing

e) Decreased diffusing capacity

f) Extremely abnormal ventilation perfusion ratio

- low Va /Q → Physiologic shunt in some parts of lung lead to poor aeration of blood .

- high Va/Q → Physiologic dead space in some parts lead to wasted ventilation.

g) Increase in pulmonary vascular resistance

Persistent reduction in forced expiratory flow rates is the most characteristic finding in COPD. Increases in the residual volume and the residual volume/total lung capacity ratio, non-uniform distribution of ventilation, and ventilation-perfusion mismatching also occur. Airflow limitation or airflow obstruction is determined by spirometry, which involves forced expiratory manoeuvres after the subject has inhaled to total lung capacity[28].

Patients with airflow obstruction related to COPD have a persistently reduced ratio of FEV_1/FVC. The reduced FEV_1 in COPD does not respond to inhaled bronchodilators. Airflow during forced exhalation is the result of the balance between the elastic recoil of the lungs promoting flow and the resistance of the airways limiting flow. In normal lungs, as well as in lungs

affected by COPD, maximal expiratory flow diminishes as the lungs empty because the lung parenchyma provides gradually less elastic recoil and because the cross-sectional area of the airways falls, raising the resistance to airflow.

In COPD there is "air trapping" (increased residual volume and increased ratio of residual volume to total lung capacity) and progressive hyperinflation (increased total lung capacity) during the final stages of the disease. Hyperinflation of the thorax during tidal breathing conserves maximum expiratory airflow, because as lung volume increases elastic recoil pressure increases, and airways enlarge so that airway resistance decreases.

The PaO_2 usually remains near normal until the FEV_1 is decreased to ~50% of predicted, and even much lower FEV_1 values can be associated with a normal PaO_2, at least at rest.

A rise of arterial level of carbon dioxide ($PaCO_2$) does not occur until the FEV_1 is <25% of predicted. Pulmonary hypertension severe enough to cause corpulmonale and right ventricular failure due to COPD typically occurs in individuals who have marked decrease in FEV_1 (<25% of predicted) and chronic hypoxemia (Pa_{O2}<55 mmHg)

Pathology:

Changes in Large Airway:

Cigarette smoking often results in mucous gland enlargement and goblet cell hyperplasia leading to cough and mucus production. There is bronchial wall

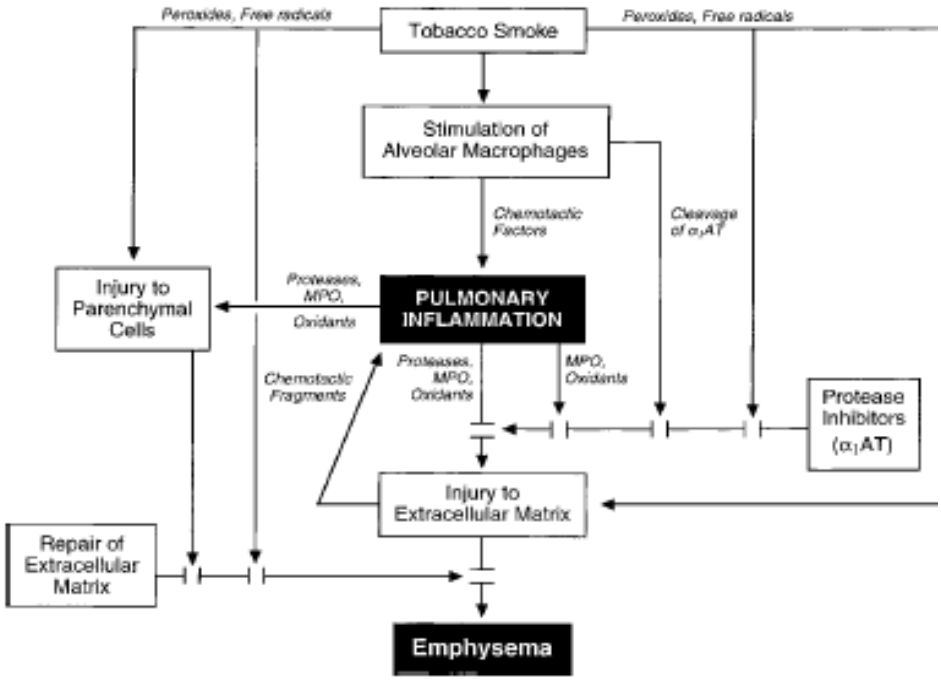
inflammation and fibrosis. Patients have smooth-muscle hypertrophy and bronchial hyper reactivity leading to airflow limitation. Neutrophil influx has been associated with purulent sputum of upper respiratory tract infections. Independent of its proteolytic activity, neutrophil elastase is among the most potent secretagogues identified.

Changes in Small Airways

The major site of increased resistance in most individuals with COPD is in airways $\leq$2 mm diameter. Characteristic cellular changes include goblet cell metaplasia, with mucus-secreting cells which replaces surfactant-secreting Clara cells. There is mononuclear phagocytes infiltration and smooth-muscle hypertrophy. These cause luminal narrowing by fibrosis, excess mucus, edema, and cellular infiltration. Reduced surfactant may increase surface tension at the air-tissue interface, predisposing to airway narrowing or collapse. Respiratory bronchiolitis with mononuclear inflammatory cells collecting in distal airway tissues may cause proteolytic destruction of elastic fibers in the respiratory bronchioles and alveolar ducts where the fibers are concentrated as rings around alveolar entrances.[32]

Because small airway patency is maintained by the surrounding lung parenchyma that provides radial traction on bronchioles at points of attachment to alveolar septa, loss of bronchiolar attachments as a result of extracellular matrix destruction may cause airway distortion and narrowing in COPD.

FIGURE - 2



Changes in Lung Parenchyma

Emphysema is defined **pathologically by The National Heart, Lung, and Blood Institute** as," an abnormal condition, permanent enlargement of distal airspaces, distal to the terminal bronchiole accompanied by destruction of their walls and without obvious fibrosis".

Emphysema is characterized by destruction of gas-exchanging air spaces, i.e., the respiratory bronchioles, alveolar ducts, and alveoli leading to loss of lung elasticity. Their walls perforate and later obliterate that result in coalescence of small distinct air spaces into abnormal and much larger air

spaces. Macrophages accumulate in respiratory bronchioles of essentially all young smokers.

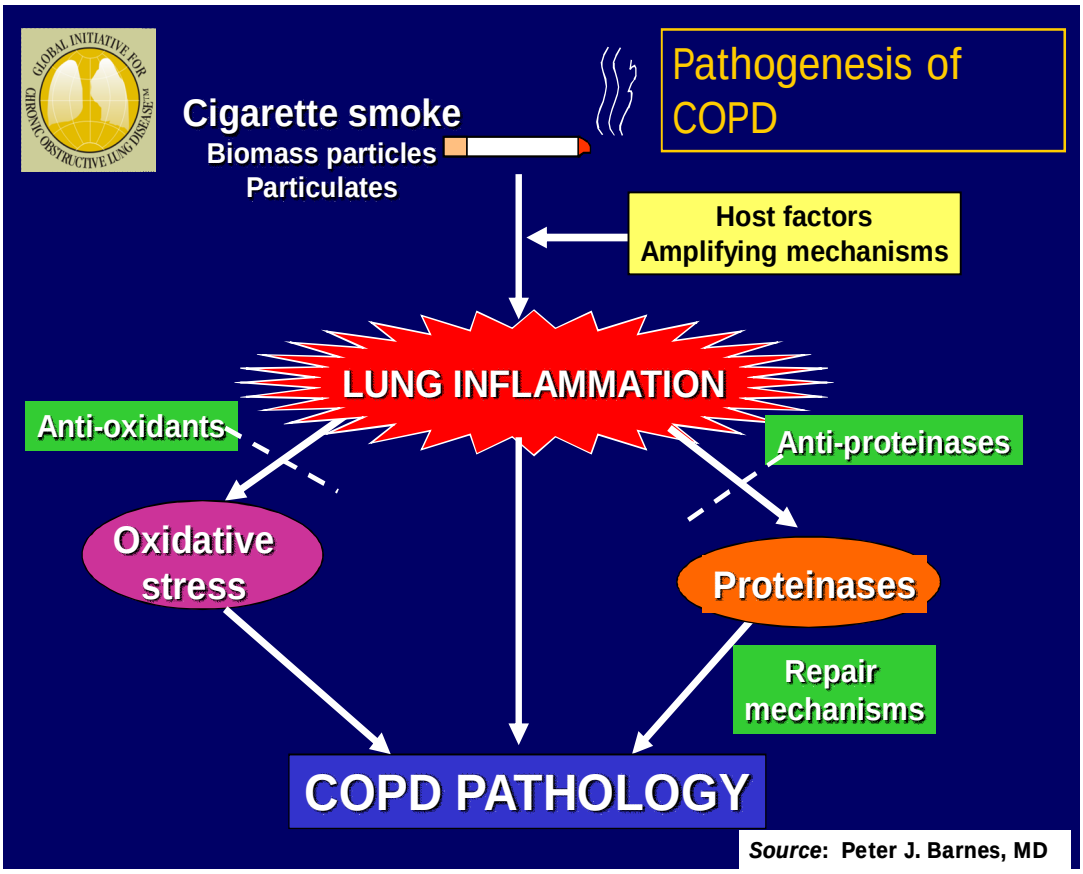
Emphysema is classified into distinct pathologic types, the most important being centriacinar and panacinar emphysema.

Centriacinar emphysema, the type most frequently associated with cigarette smoking, is characterized by enlarged air spaces found (initially) in association with respiratory bronchioles. It is most prominent in the upper lobes and superior segments of lower lobes and is often quite focal. It is most common in males.

Panacinar emphysema refers to abnormally large air spaces evenly distributed within and across acinar units. It is usually observed in patients with α_1AT deficiency, which has a predilection for the lower lobes.

FIGURE - 3

PATHOGENESIS OF COPD



Pathogenesis:

Airflow limitation, the major physiologic change in COPD can result from both small airway obstruction and emphysema. Fibrosis surrounding the small airways appears to be a significant contributor. Collagen accumulation around the airways in the face of increased collagenase activity remain an enigma. Proteinase can predispose to fibrosis, including proteolytic activation of transforming growth factor (TGF).

The dominant concept of the pathogenesis of emphysema comprises of four interrelated events.

(1) Chronic exposure to cigarette smoke may lead to inflammatory cell recruitment within the terminal air spaces of the lung.

(2) These inflammatory cells release elastolytic proteinases that damage the extracellular matrix of the lung.

(3) Structural cell death results from oxidant stress and loss of matrix-cell attachment.

(4) Ineffective repair of elastin and other extracellular matrix components result in air space enlargement that defines pulmonary emphysema.

Chronic Bronchitis is defined **clinically by The British Medical Research Council** as," presence of chronic productive cough on most of the days for three months, in each of two consecutive years in a patient in whom other causes of chronic cough has been excluded". Diagnosis is based on the history of excessive expectoration of mucus.

Disease Process	Anatomic Location of Lesion	Cause of Reduced Airflow
Chronic bronchitis	Large and small (<2-mm diameter) airways	Narrowing of airways by fibrosis, secretions, edema
Emphysema	Lung parenchyma	Loss of lung elastic recoil

THE ELASTASE:ANTIELASTASE HYPOTHESIS

Patients with genetic deficiency in α_1AT, the inhibitor of the serine proteinase neutrophil elastase, were at increased risk of emphysema, and instillation of elastases, including neutrophil elastase to experimental animals resulted in emphysema. The elastase : antielastase hypothesis remains a main mechanism for the development of emphysema. However, a complex network of immune and inflammatory cells and additional proteinases that contribute to emphysema have subsequently been identified.

INFLAMMATION AND EXTRACELLULAR MATRIX PROTEOLYSIS

On exposure to oxidants from cigarette smoke, macrophages in the lower air space become activated, producing proteinases and chemokines that attract other inflammatory cells via oxidant-induced inactivation of histone deacetylase-2, shifting the balance toward acetylated or loose chromatin, exposing nuclear factor B sites and resulting in transcription of matrix metalloproteinases, proinflammatory cytokines such as interleukin 8 (IL-8), and

tumor necrosis factor (TNF). This leads to recruitment of neutrophils. CD8+ T cells are also recruited in response to cigarette smoke and release interferon inducible protein-10 (IP-10, CXCL-7) that in turn lead to production of elastase by macrophages (Matrix metalloproteinase-12). Matrix metalloproteinases and serine proteinases, most notably neutrophil elastase, work together by degrading the inhibitor of the other, leading to lung destruction. Proteolytic cleavage products of elastin also serve as a macrophage chemokine, fueling this destructive positive feedback loop. Autoimmune mechanisms promote the progression of disease. Increased B cells and lymphoid follicles are present in patients with advanced disease. Antibodies have been found against elastin fragments. IgG auto antibodies with more affinity for pulmonary epithelium and the potential to mediate cytotoxicity have been detected.

Concomitant cigarette smoke–induced loss of cilia in the airway epithelium and impaired macrophage phagocytosis predispose to bacterial infection with neutrophilia. In end-stage lung disease, long after smoking cessation there remains an exuberant inflammatory response, suggesting that mechanisms of cigarette smoke–induced inflammation that initiate the disease differ from mechanisms that sustain inflammation after smoking cessation.

Air space enlargement with loss of alveolar units obviously requires disappearance of both extracellular matrix and cells. Cell death can occur from increased oxidant stress both directly from cigarette smoke and from inflammation. Animal models have used endothelial and epithelial cell death as a means to generate transient air space enlargement. Uptake of apoptotic cells

by macrophages results in production of growth factors and dampens inflammation, promoting lung repair. Cigarette smoke impairs macrophage uptake of apoptotic cells, limiting repair.

The ability of the adult lung to repair damaged alveoli appears limited. It is unlikely that the process of septation that is responsible for alveologenesis during lung development can be reinitiated. The capacity of stem cells to repopulate the lung is under active investigation. It appears difficult for an adult human to completely restore an appropriate extracellular matrix, particularly functional elastic fibers.

Clinical Presentation:

History:

The three most common symptoms are cough, sputum production. Activities involving significant arm work, particularly at or above shoulder level, are particularly difficult for patients with COPD. In the most advanced stages, patients become breathless after doing simple activities of daily living.

GUIDE TO RATING SEVERITY OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

	Mild	**Moderate**	**Severe**
typical symptoms	few symptoms	increasing dyspnoea	dyspnoea on minimal exertion
	breathlessness on moderate exertion	breathlessness walking on level ground	daily activities severely curtailed
	little or no effect on daily activities	cough and sputum production	chronic cough
		infections requiring steroids	
lung function	$FEV_1 \approx$ 60-80% predicted	$FEV_1 \approx$ 40-59% predicted	$FEV_1 <$ 40% predicted

Physical Findings:

In the early stages of COPD, patients have a normal physical examination. Current smokers may have signs of active smoking such as an odour of smoke or nicotine staining of fingernails. In severe disease, there is prolonged expiratory phase with expiratory wheezing. Signs of hyperinflation include a barrel chest and enlarged lung volumes with poor diaphragmatic excursion as assessed by percussion. Patients with severe airflow obstruction may also exhibit use of accessory muscles of respiration, sitting in the

characteristic "tripod" position to facilitate the actions of the sternocleidomastoid, scalene and intercostal muscles. Patients may have cyanosis that is visible in the lips and nail beds. Pink puffers," are thin and noncyanotic at rest and have prominent use of accessory muscles. Patients with chronic bronchitis are more likely to be heavy and cyanotic ("blue bloaters). Most patients have elements of both bronchitis and emphysema and that the physical examination does not reliably differentiate the two entities.

Advanced disease may be accompanied by systemic wasting, with significant weight loss, bitemporal wasting, and diffuse loss of subcutaneous adipose tissue. This syndrome has been associated with both inadequate oral intake and elevated levels of inflammatory cytokines (TNF). Such wasting is an independent poor prognostic factor in COPD.

Laboratory Findings:

The characteristic feature of COPD is airflow obstruction. Pulmonary function testing shows airflow obstruction which is more for expiration than inspiration, with resultant increased work of breathing.

There is reduction in FEV_1 and FEV_1/FVC. With worsening disease severity, lung volumes may increase resulting in an increase in total lung capacity, functional residual capacity, and residual volume. In patients with emphysema, the diffusing capacity may be reduced, reflecting the lung

parenchymal destruction characteristic of the disease. There is decrease in maximum expiratory flow rates and uneven ventilation. The degree of airflow obstruction is an important prognostic factor in COPD and is the basis for the Global Initiative for Lung Disease (GOLD) redundant classification.

A multifactorial index incorporating airflow obstruction, exercise performance, dyspnea, and body mass index is a better predictor of mortality rate than pulmonary function alone.

SPIROMETRY

It means ‘‘the measuring of breath’’. This is a test for dynamic ventilatory functions of lung. The spirometer is an instrument used for these tests and the procedure is called spirometry. It is an essential tool in the hands of the physician to aid in the evaluation, diagnosis, and management of respiratory disorders. Graphical recording of spirometry is called **spirogram.**

Types of spirometer

A. Volume-Displacement spirometers

B. Flow sensing spirometers or Pneumotachometer

Flow sensing spirometers are portable, easy to maintain and is most widely used. Portable flow sensing spirometer working on the infra red interruption principle was used in the present study to categorize the patients into different stages.

The patient is asked to take the deepest breath they can, and then exhale into the sensor as hard as possible, for as long as possible, preferably at least 6 seconds. Soft nose clips may be used to prevent air escaping through the nose. Filter mouthpieces may be used to prevent the spread of microorganisms.

PULMONARY FUNCTION TESTS

Various pulmonary function tests are being carried out to make proper assessment of lung function non invasively. Pulmonary function tests aim at assessing the various aspects of ventilation, diffusion and perfusion.

I) Ventilation related parameters

Lung volumes and capacities.

II) Ventilation–Perfusion related parameters

a. Pulmonary blood flow.

b. Ventilation/ perfusion ratio.

III) Diffusion related parameters

a. Diffusing capacity of lung for oxygen **(D_LO_2).**

b. Diffusing capacity of lung for carbon monoxide **(D_LCO).**

IV) Tests for Mechanics of Breathing

a. Elastic resistance (Compliance and Elastance).

b. Non-elastic tissue resistance.

c. Airway resistance.

Pulmonary function tests were performed using a dry spirometer device (Erich Jaeger Gmb H, Hoechberg, Germany) after inhaling salbutamol (Ventolin, GlaxoSmithKline, London, UK) as classification of severity of COPD in GOLD guidelines is based on post bronchodilator FEV_1. Each subject underwent a forced spirometry to obtain the following parameters:

Forced vital capacity (FVC),

Forced expiratoryvolumein1s (FEV_1)and

FEV_1/FVC ratio.

Subjects with FEV_1 higher than 50% predicted but lower than 80% predicted were classified as the **mild-to-moderate group;** subjects with FEV_1 lower than 50% predicted were classified as the **severe group** according to **Global Initiative for Chronic Obstructive Lung Disease 2010 criteria.** FEV_1 value is a powerful predictor of mortality. Also FEV_1/FVC and FEF_{25} were found to be the best predictors of longitudinal decline in lung function in men. Blood gases analysis is a better predictor of mortality rate than pulmonary function .

GOLD-TABLE

1) Mild: Post-bronchodilator $FEV_1 \geq 80\%$ predicted

2) Moderate: Post-bronchodilator $FEV_1 \geq 50\%$ but <80% predicted

3) Severe: Post-bronchodilator $FEV_1 \geq 30\%$ but <50% predicted

4) Very Severe: Post-bronchodilator $FEV_1 < 30\%$ predicted

Lung Volumes and Capacities

Static volumes:

Tidal volume:

It is the volume of air that moves in and out of the lungs during normal quiet breathing. It is about 500ml.

Inspiratory reserve volume (IRV):

It is the amount of air that can be inspired above the tidal volume by maximum effort. It is about 2500ml.

Expiratory reserve volume:

It is the amount of air that be forcefully expired above the normal tidal expiration. It is about 1100ml.

Residual volume:

It is the amount of air that remains in the lungs after a maximal voluntary expiration. The lungs are not completely emptied of air because the distal airways collapse with air trapped inside due to increase in external pressure.

Residual volume can be expelled only by opening the thoracic cage and causing collapse of the lungs. It is about 1200ml.

The lungs are not completely emptied of air even after complete collapse because of the air trapped inside the alveoli. This is the **minimal volume or minimal air**. This air makes the lung tissues to float in water (**Swammeredam, 1664).**

Closing volume: This is the volume at which the peripheral small airways begin to close during a forced expiration. This occurs when 10% of the vital capacity is left in the lungs. Closing volume is increased in obstructive lung disease.

Dynamic volumes:

Respiratory minute volume (pulmonary ventilation):

This is the volume of air that is inspired or expired during one minute. At rest it is about 6 litres.

Maximum voluntary ventilation:

It is the maximum amount of air that can be moved in or out of the lungs by voluntary effort. It is about 125-170 L/min.

Static capacities:

Vital capacity: Forced vital capacity (FVC):

It is the maximum volume of air that can be expelled rapidly by maximal effort following a deep inspiration. (It is equal to tidal volume + Inspiratory reserve volume + Expiratory reserve volume). It is about 3.5 – 5.5 litres. It is a good index to assess pulmonary function and strength of the muscles of respiration.

Inspiratory capacity:

It is the maximum amount of air that a person can breathe in by forced inspiration after a normal expiration. It is about 3000ml.

Functional Residual capacity (FRC):

It is the volume of air in the lungs at the end of quiet expiration. It is about 2500ml. The FRC acts as a buffer against fluctuations in PaO_2 and $PaCO_2$ in the respiratory cycle, enabling continuous gas exchange. It reduces the load on the respiratory system and the left ventricle.

Total Lung Capacity (TLC):

It is the volume of air that is present in the lungs after a deep, maximal inspiration. It is about 4500 - 6000ml.

Dynamic capacities:

Timed vital capacity- FEV_1:

It is the forced expiratory volume in the first second. This is the fraction of the FVC expelled in the first second during a forced expiration. In a normal individual 80-85%of the FVC is expired in the first second (FEV_1), 95% in two seconds (FEV_2) and 97-100% in three seconds (FEV_3). It is reported as volume in litres, even though it denotes volume over a specific time.

FEV_1%:

FEV_1 expressed as a percentage of FVC gives **FEV_1%.**

FEV_1% = FEV_1/FVC X 100.

Normal Values:

Young adults : 80-85%.

Elderly people : 70-80%.

Children : >90%.

In restrictive lung disorders, FVC & FEV_1 are reduced. FEV_1% is normal or even above normal.

In obstructive lung disorders FEV_1 is reduced and FVC is very much reduced. So FEV_1% is also reduced.

Maximum Mild Expiratory Flow Rate (MMEFR) or Mean Forced Expiratory Flow $_{25-75\%}$ (FEF $_{25-75\%}$):

This is the mean flow rate achieved during the middle 50% of FVC. This indicates the patency of small airways.

Maximal Expiratory Flow Volume (MEFV) Curves and Maximal Forced Expiratory Flow Rates:

It is a graphical representation of maximum flow rate against lung volume during FVC performance. The values derived are FEF_{25}, FEF_{50} and FEF75. It is helpful to differentiate between central and peripheral airway disease.

Peak Expiratory Flow Rate (PEFR):

This is the rate of maximum airflow out of the lungs which is sustained for 10 milliseconds during a forceful sudden expiration following a maximum inspiration. It is expressed in litres per minute or litres per second. This is decreased in obstructive and restrictive lung disorders.

Normal values:

Age group	**PEFR (L/min)**	
	Male	**Female**
<40 years	400-650	250-450
>40years	300-500	200-400

Inspiratory Volumes and Flow rates:

Inspiratory Vital Capacity (FIVC), Forced Inspiratory Volumes and Flow Rates (FIV & FIF) and Maximum Inspiratory Flow Volume (MIFV) Curves can also be derived. They are useful in detecting extrathoracic airway obstruction.[31]

Breathing Reserve or Dyspnoeic Index:

BR% = MVV – RMV/MVV X 100.

Normal breathing reserve is > 90%.

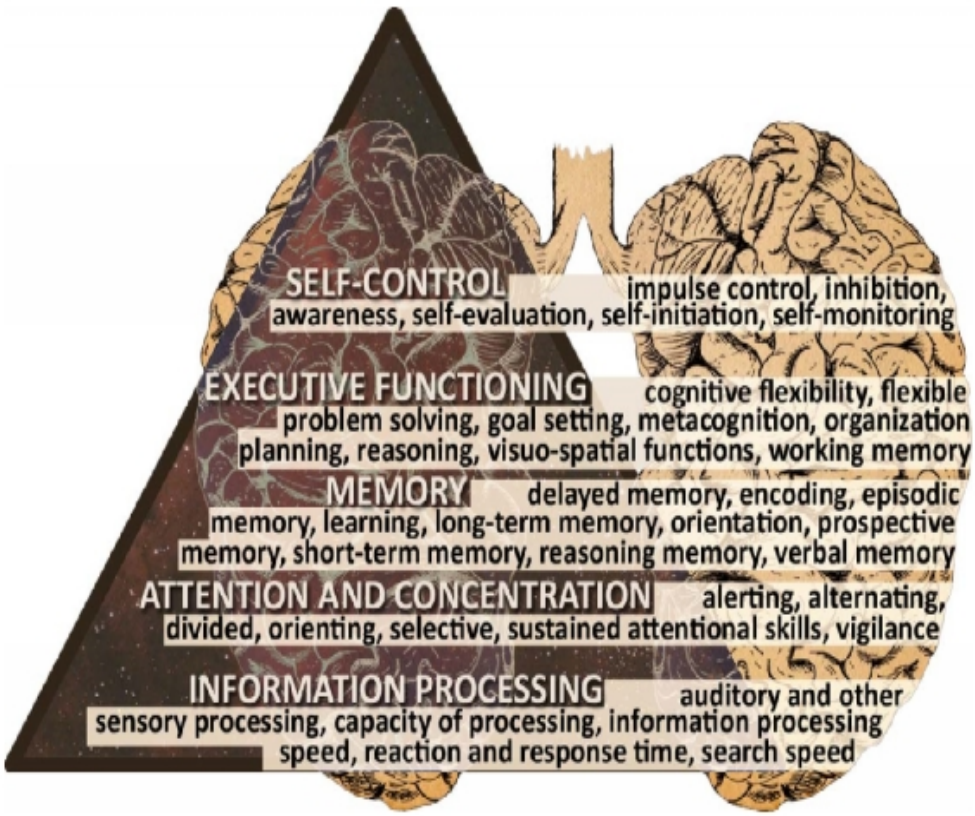
COGNITION:

The term cognition is derived from the latin term `Cognoscere' meaning to know or to conceptualise which includes the functions involved in synthesizing information, that is perception, attention, memory, language, and reasoning. Cognition means knowledge or understanding. Cognitive functions decide our success, competence and healthy living. Cognitive psychology is more scientific, and seeks highly specific and detailed answers to precise questions, concerned with conscious mental life, and studies inner processes. Cognition includes a wide range of human mental abilities. It is the third main area of human development in addition to physical and social development. Cognitive or mental development not only includes intelligence, but also complementary processes such as perceiving, recognizing, recalling and interpreting information as well as all forms of reasoning. Cognitive ability is usually broken down into domains concerning memory, learning ability,

attention/concentration, abstract thinking, and problem solving.[35] The thinking process occurs in the brain from the sensory input received, and the stored memory which brings on appropriate motor activity.

FIGURE - 4

COGNITION DOMAINS AND SPECIFIC FUNCTIONS



Executive function is the function of dorsolateral prefrontal cortex. Executive functions play a role in planning and initiation of independent activities, self monitoring, and performance, switching between tasks, inhibition of inappropriate responses and planning complex motor and problem solving responses[36]. Although prefrontal cortex has long been explained as a substrate

for executive functions, more recent and advanced research has led to the discovery of increased role played by extreme interconnections between subcortical and cortical regions of brain. Executive functions are key to our capacity, formulating our goals, planning and organising such goal directed behaviours, carrying out such behaviours fully and effectively and monitoring and self correcting ones behaviour as needed[37]

Attention or Vigilance is the ability to maintain attention over time. Verbal learning and memory is the ability to learn more information, to retain newly learned information over time, and recognising previously presented material. Verbal fluency is the ability to produce as many words as possible. Immediate or Working memory is the ability to hold a limited amount of information for a brief period of time. Working memory is the core component of neurocognition, which is mediated by prefrontal cortical regions. Development of thought in a child was studied by **Jean Piaget** in 20th C, an eminent Swiss epistemologist.

Knudsen[38] describes a model which shows four processes of attention with working memory in the centre.

1. Working memory temporarily stores information for analysis.

2. Competitive selection that determines which information goes to working memory.

3. Top-down sensitivity control by the content of working memory which influences the selection of new information. This results in voluntary control of attention in a recurrent loop – endogenous attention

4. Bottom-up filters which automatically enhance the response to infrequent stimuli – exogenous attention.

The term "working memory" was coined by **Miller, Galanter and Pribram.**[39] Most working memory tasks recruit a network of prefrontal cortex and parietal areas. During a working memory task, the connectivity between these areas increases.[40]

Working memory is a special short term memory store. It has three component systems (**Baddley and Hitch model**)**:**

a) Attentional control system: It focuses on perception of specific happenings in the environment. It is located in the prefrontal cortex and has very limited capacity. It regulates the flow of information to two rehearsal systems which are thought to sustain memory for temporary use.

b) Rehearsal systems- Articulatory loop: It refers to a storage system with a quickly fading memory trace. Here, memory for numbers and words can be sustained by subvocal speech e.g remembering a new mobile number as a person prepares to dial it.

c) **Visuo-spatial sketch pad:** It represents both the spatial location and the visual properties of object to be remembered. For example, this system allows a person to store the image of an individual's face whom he met at a dinner party.

The two rehearsal systems are situated in the posterior association areas. The information processed in either of these systems has the possibility of reaching long term **memory.** The cognitive state examination includes orientation, attention, concentration, memory, general information, ad intelligence.

NEUROPSYCHOLOGICAL TESTS

Mini Mental State Examination (MMSE):

MMSE (**FOLSTEIN** et al., 1975)[41] takes 5-10 mins to administer and test retest reliability is high. It provides a rough and ready index of cognitive functioning. First part covers orientation, attention, concentration and memory. Second part tests the ability to name common objects, follow verbal or written commands, write a sentence spontaneously and copy a simple figure (eg: overlapping pentagons) - visuospatial testing.

The total score is 30[42], scores less than 24 indicates cognitive impairment.

Stroop Test: (Stroop Color and Word Test)

The basic aspect provided by the Stroop is that it has been associated with cognitive flexibility, resistance to interference from outside stimuli, creativity, psychopathology, and cognitive complexity. It clearly plays a role in many interrelated cognitive processes which determine an individual's ability to successfully cope with cognitive stress and to process complex input (Golden, 1978).

Inhibitory processing is the efficiency of the inhibitory process that underlies selective attention. Inhibition allows a reduction of irrelevant information to enter working memory (Hasher & Zacks, 1988). The area of the brain which is usually affected by inhibition is the frontal lobe. The test involves multiple areas including knowledge, attention, visual scanning and acuity. As the impairment in executive function severely affects the quality of life, the rehabilitation measures should be directly targeted on management of executive functions after quantifying the problem (Crawford 2000)[43]. **John Ridley Stroop** (1935) worked on the interference that can arise between word reading and colour naming. It takes longer time to read printed colour names when they are printed in coloured ink different from that of the coloured word. This may be due to

1) response conflict

2) failure of response inhibition

3) failure of selective attention.

The increase in time taken to perform the second task compared with the first task is referred to as "**the Stroop interference effect**" (e.g., **Davidson, Zacks, & Williams, 2003; Moering, Schinka, Mortimer, & Graves,** 2003). It gives selective attention, cognitive flexibility and control, self correction and speed of processing (**Uttl & Graf**, 1997) or executive functioning (**Moering** et al., 2003).

Slowing with age has been consistently documented (Hasher & Zacks, 1988; Obler and Albert, 1985; Spreen and Strauss, 1991). The results also reinforce the slowing due to decreased oxygen supply to the brain as identified in those with COPD (Clark).

COGNITIVE EVOKED POTENTIAL STUDY

Evoked potentials refer to the action potentials generated from central nervous system in response to a specific and adequate stimulus. They are small and are buried in the background of spontaneous electrical activity (EEG). Their details can only be studied and evaluated by repeated stimulation and averaging the responses obtained after each stimulation. Evoked potentials have evolved from a challenging scientific technique to a commonly applied tool in the neurophysiology in the last few decades[44]. They establish objective evidence of abnormality when signs and symptoms are equivocal.

Evoked potentials are classified into

1. Stimulus related potentials

2. Event related potentials (ERP) or Endogenous potentials [23]

Stimulus related potentials:

They are generated in response to an exogenous stimulus – visual, auditory, and somatosensory. They depend on the physical characteristics of the stimulus. Commonly used stimulus related potentials are brainstem evoked response audiometry, visual evoked potential and somatosensory evoked potential.

Event related potentials:

In **1935-1936, Pauline and Hallowell Davis** recorded the first known ERPs on awake humans. In 1964**, Grey Walter** and colleagues reported cognitive ERP component, called the contingent negative variation (CNV). **Sutton, Braren, and Zubin** (1965) made advancement with the discovery of the P_3 component. In 1980s, the introduction of inexpensive computers opened up a new door for cognitive neuroscience research. Currently, ERP is one of the most widely used methods in cognitive neuroscience research to study the physiological correlates of sensory, perceptual and cognitive activity associated with processing information.

Over the past few decades, electrophysiology has contributed substantially to the understanding of normal as well as abnormal brain function deviations in psychopathological conditions. Electrophysiological techniques enable the study of the physiology of brain's systems with a high temporal

resolution, providing the best methods to describe the time course of brain-electrical activation during complex cognitive processes (such as conscious sensory discrimination or semantic processing). They are elicited when the subject is required to distinguish one stimulus (the target) from the other (non-target). Since ERPs are related to cognitive processing associated with the distinction of target from non-target stimuli, they are also called cognitive evoked potential. ERPs are also referred to as P_{300}, because they occur after a latency period of approximately 300 milli seconds[45,46]. ERPs are independent of the physical characteristics of the stimulus. When a stimulus is presented to the brain, it travels through the receiving sensory organ and the brainstem (except for visual and olfactory stimuli) on its way to the primary cortical regions mediating this particular sensory modality. ERPs recorded over primary sensory cortex indicate how the stimulus was received and recorded by the brain, thereby providing an index of the integrity of the underlying neural architecture. For instance, the early waves arising immediately after (within about 15 ms) an auditory stimulus are referred to as **the brainstem auditory evoked potential.** These components reflect the intactness of the pathways that they traverse, are useful for the diagnosis of sensory defects (such as hearing loss), and thus are of great interest to neurologists.

Once received by the brain, a stimulus undergoes psychological processing and evaluation, and these operations are reflected in later ERP waves that are distributed to various scalp locations. These components are influenced by levels of arousal and attention as well as the informational content and

salience of the stimulus. These long latency evoked potentials are related to cognitive processing and so are called as cognitive evoked potentials, event related potential, $P_{3,}$ P_{300} or endogenous EP. Because many of these components have been shown to be sensitive to particular experimental manipulations, various paradigms have been developed to facilitate the study of specific waveforms. An **event-related potential** (**ERP**) is the measured brain response that is the direct result of a specific sensory, cognitive, or motor event. It is any stereotyped electrophysiological response to a stimulus. It provides a noninvasive means of evaluating brain function in patients with cognitive diseases.

The characteristic features of ERPs are,

1) They are elicited by endogenous stimuli

2) Requires attention and patients cooperation

3) They have a longer latency, higher amplitude, and lower frequency of waveform.

4) They are not influenced by frequency and intensity of stimuli

They are less bound by the physical properties of a stimulus than sensory ERPs. The characteristics of late waves reflect individual differences in how the stimulus interacts with and affects the person. Various features of ERP have been found to be highly heritable, indicating that they capture stable individual differences in electrophysiology. Late ERP components also have been shown

to be deviant in many clinical and psychiatric conditions and thus are of considerable interest for their potential as clinical tools. The P_{300} is best recorded with an analog high-pass filter set at 0.1 Hz or less[47]

Ocular Artifacts:

Electrical potentials generated by eye movements and blinks are a major problem when recording the P_{300} wave. Subjects are instructed not to blink or move their eyes unless absolutely necessary. The P_{300} wave is usually measured in terms of a peak amplitude relative to a prestimulus baseline and a peak latency relative to the stimulus onset. The peak is usually identified as the most positive point in the waveform between 200 or 250 ms and some later time.

The measurements are usually taken at one electrode location, typically either cz or pz. The latency of the P_{300} wave varies from one electrode location to the next, usually being earlier at more frontal locations and the amplitude of the P_{300} wave varies with the amount of conscious attention paid to a stimulus. The P_{300} wave generally occurs only in response to task-relevant stimuli. The amplitude of the P300 wave was inversely proportional to the probability of each tone.

Goodin et al. (1978a) reported that the latency of P_{300} wave in an auditory oddball paradigm was significantly related to the age of subjects between 18 and 76 years.

In general, the amplitude of the P_{300} is smaller in older subjects and it increases with increasing age until about 13yrs, after which it may decrease slightly to normal adult values (**polich). T**he P_{300} wave is not generated in one place. It may represent concurrent activity in multiple regions of the brain.

The regions of the brain most involved in this interactive process would be the polymodal association areas of the frontal, parietal, temporal lobes and the limbic system.

A normal P_{300} wave may therefore indicate that a subject is cognitively processing the evoking stimulus. This may be helpful in demonstrating the brain's ability to discriminate between stimuli in cases of functional sensory impairment. If the P_{300} wave is abnormally small or delayed, there is probably some abnormality of cognitive processing. Latency is a much more reliable indicator than amplitude, since latency is difficult to alter with attention. Furthermore, the normal limits for latency are less broad than the normal limits for amplitude. The use of the P_{300} latency to demonstrate cognitive dysfunction is important in such conditions as early dementia or the cognitive dysfunction that occurs with metabolic disorders have higher amplitude and lower frequency compared to the stimulus related potentials.

Physiological Basis of Waves

Any stimulus like auditory, visual, olfactory, somatosensory or pain can be used for eliciting cognitive potential. Auditory stimuli are most frequently used in clinical practice. The stimuli are delivered using standard odd ball

paradigm where two types of stimuli: target (infrequent) and non-target (frequent) are used. The target stimuli comprise 15 – 20 % of total stimuli, which appear randomly. The character of target stimuli differs from the common stimuli in terms of frequency or intensity. The patient is asked to count mentally or raise the finger or press a button in response to target stimuli. This specific intellectual function produces discrete waveforms of cognitive evoked potential.

ERPs are wave patterns with 3 parameters

1) Polarity

2) Latency

3) Scalp distribution

Amplitude (μV) is the difference between the mean prestimulus baseline voltage and the largest positive or negative peak of the ERP waveform within a time window.

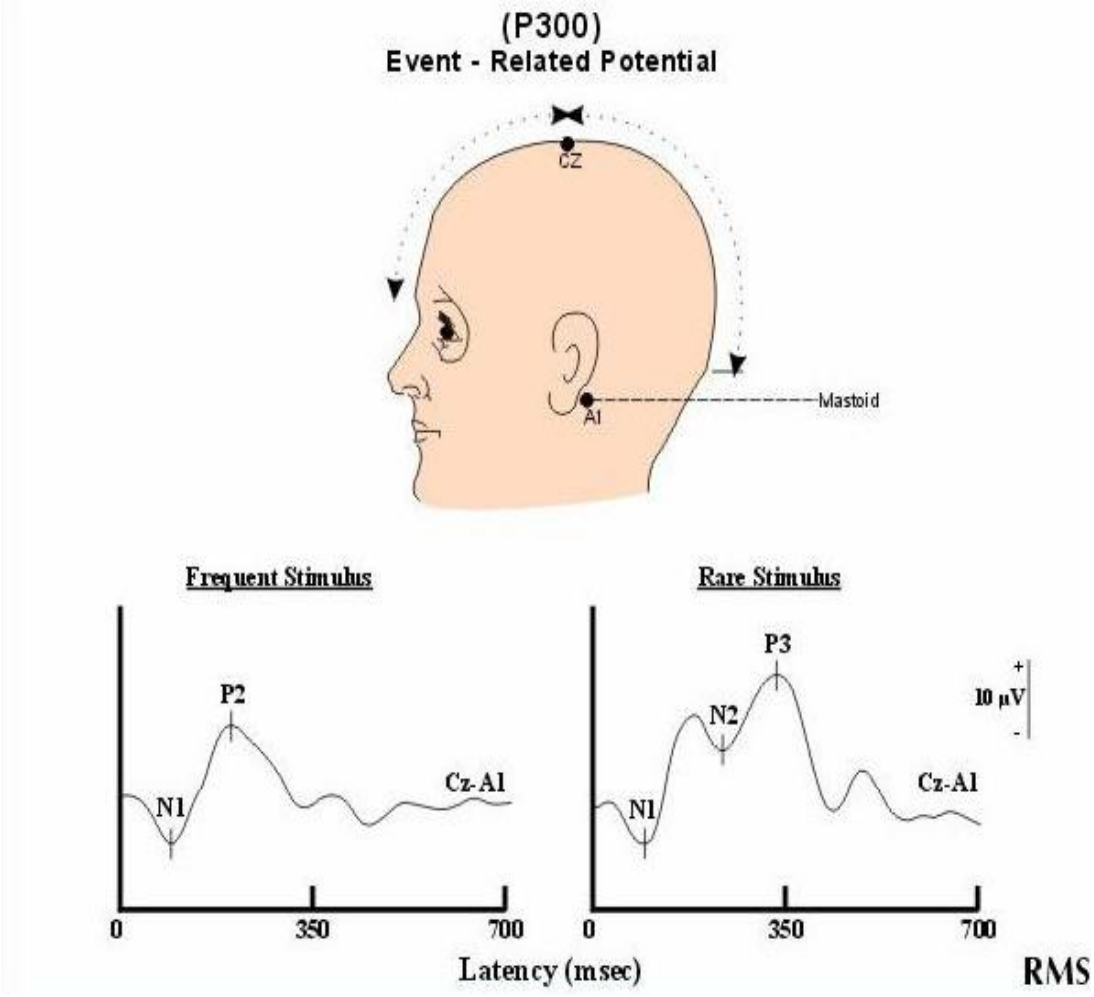
Latency (ms) is the time from stimulus onset to the point of maximum amplitude (Polish, 2007). The positive and negative wave forms are designated as P and N respectively followed by approximate latency in milli seconds. There are two negative waves, N_{100} and N_{200} and two positive waves, P_{200} and P_{300} (fig:5). These waves reflect specific cognitive processes. The N_{100} and P_{200} waves are considered to reflect early attention capacities related to stimulus processing[48]**.** The N_{200} wave is regarded as an index of stimulus detection[49]**.**The

P_{300} wave reflects a later, more controlled and voluntary decision making capacity and memory[50].

The P_{300} wave is the most frequently investigated ERP. It is related to the maintenance of working memory (Donchin and Coles, 1988). P_{300} reflects the mnemonic and cognitive function in humans[51,52], information processing[53], and seems to be strongly associated with short term memory[54].

FIGURE : 5

WAVES IN COGNITIVE EVOKED POTENTIAL



Generators of P $_{300}$:

Different areas of the brain such as inferior parietal lobule, frontal lobe, hippocampus, median temporal lobe, insula and other limbic structures are involved in generation of P_{300}[23]. The involvement of dopaminergic system at these sites in the generation of P $_{300}$ is well documented[55]**.**

P $_{300}$ Latency And Amplitude:

There are two ways of measuring P $_{300}$ latency [23]

1. Point of maximum P $_{300}$ amplitude
2. Intersectional extrapolation – The ascending and descending limbs of P $_{300}$ wave are extended to the point of intersection which is measured as P $_{300}$ latency.

The amplitude of P $_{300}$ wave is measured from pre stimulus base to peak or peak to peak from N_{200} wave. Generally P $_{300}$ amplitude decreases as the latency increases[56]**.**

VARIABLES AFFECTING P $_{300}$

1. Attention

Decrease in alertness is associated with reduction in amplitude[57]. Drowsiness or inattention decreases P $_{300}$ amplitude or may even obliterate it.

However P_{300} can be recorded in stage II sleep, but disappears in slow wave sleep[58]. P_{300} amplitude increases with correctly recognised stimuli compared to incorrect ones[55].

2. Age

The P_{300} latency increases as age increases. There is increase in mean latency by about 1 – 1.5 milli second per year after the age of 20 years (Goodin et al1978a)[59]. P_{300} is lowest in the age group 15 – 25 years[60]. The amplitude decreases after the age of 80 years.

3. **Body mass index**

Prolonged P_{300} latency and decreased amplitude was observed in obese individuals by Tascilar et al[61] .

4. Drugs

Anticholinergics and antihistaminics increase P_{300} latency and reduce its amplitude (Callaway, 1984; Hammond et al.,1987; Meader et al., 1989)[62]. Physostigmine can reverse the effect of anticholinergic on P_{300}.

5. Technical Parameters

Stimulus intensity generally does not influence P_{300}, but a markedly high intensity may reduce P_{300} latency[63]. P_{300} amplitude increases as the target stimulus frequency in the global sequence decreases[64]. Use of high pass filter of

1 Hz may decrease P_{300} latency and amplitude compared to lower frequency high pass filters[65].

Clinical application of P_{300} :

A normal **P_{300}** indicates that a subject is cognitively processing the evoking stimulus. Goodin et al[66] were the first to show that P_{300} latency delay might provide a specific and sensitive marker for dementia. If P_{300} is small or late it indicates defective cognitive processing. The latency is a more reliable indicator than the amplitude[67]. It is **an indicator of subclinical encephalopathy.** P_{300} is an objective tool for detecting cognitive impairment[68]**.**

Clinical utility of P_{300} has been increased by identification of factors that lead to variability of P_{300} measurement. When appropriate standardised procedures are used, the P_{300} can prove to be a highly useful means to quantify cognitive capability.

Some important clinical applications of P_{300} are in dementia, cognitive disorders in children, encephalopathy, alcoholism, Parkinson's disease, Huntington's disease, HIV infection, Psychiatric disorders, Mental retardation, vitamin B_{12} deficiency, organophosphate poisoning, chronic liver failure and chronic renal failure.

Function of P_{300}

It is referred as Aha wave. In the Neuroinhibition Hypothesis, since infrequent, low probability stimuli can be biologically important, it is adaptive to inhibit unrelated activity to promote processing efficiency thereby yielding large P_{300} amplitudes. Memory is updated after incoming information has been evaluated. Cognitive theory suggests that information is processed automatically which is fast and efficient, mostly by controlled processing which is slow, effortful, conscious, and serial. All consciously controlled responses occur after and simple responses occur automatically prior to $P_{300.}$

HYPOXEMIA :

The term Hypoxia means "oxygen levels which are below atmospheric concentration. This occurs when the inspired oxygen concentration is low, thus resulting in " hypoxaemic hypoxia" or when the general barometric pressure is low it is called "hypobaric hypoxia". **Mild hypoxia** - partial pressure of oxygen (PaO2) is above 50mmHg, at this level there is complete compensation and general function is barely altered. Partial pressure of oxygen between 35 and 50 mmHg **is moderate** hypoxia, a state which leads to variable findings in cognition. When PaO2 is below35mmHg (severe hypoxia), there is loss of conscienceness. Moderate and **severe** hypoxia can result in variable neuronal loss depending on the severity and length of exposure."[69].

Pathophysiological Changes in Central Nervous System Due to Chronic Hypoxia:

Cerebral hypoxia depends on, the severity, duration, speed of onset, and progression of illness[70]. Chronic Hypoxia corresponds to the time required to trigger a physiological response. It can be from weeks to months[71]. Some patients who have normal oxygen saturation may experience hypoxic episodes after exercise[72,73], during sleep or during daily activities.[74,75]. The respiratory and sympathetic responses are the adaptation procedures leading to changes in signalling pathways, in neuromodulators, and their receptors, and in the genomic effects. Vascular adaptations is by PaO_2, Hb concentration, and Hb saturation by, increased ventilation, pulmonary vasoconstriction, increased production of red blood cells. Polycythemia increases the oxygen carrying capacity of blood and shifts the oxygen dissociation curve to right.

Cerebral blood flow is increased by neuronal pathway from brain stem and by local tissue factors like nitric oxide, adenosine, potassium ions etc and are closely linked to blood oxygen concentration[76,72,78,79,80] .

In response to hypoxia, encephalic neurons lower the metabolic rate and short and long term adaptation come into play. Depolarisation of potassium, calcium and sodium channels lead to higher cell excitability.

COGNITION IMPAIRMENT IN COPD :

In recent decades, several studies have demonstrated the presence of cognitive impairment **(Huppert F, GrantI, Prigatano, Fix, Incalzi, Vos PJE, Fioravanti M, Stuss DT, Kosaro E, Leisker JJ, Ozge, C Ozge, Lima OM).**

Lung diseases causing cognitive impairment due to chronic hypoxia has been studied and the common cognitive abnormalities observed were memory impairment[81,82,83], verbal language loss,[76] attention disturbance,[81,83,84,85,86,87] dys-executive syndrome,[86,87,88,80] and difficulties in abstract thinking[81] were found.

Low forced expiratory volume of first second (FEV_1s) and forced vital capacity (FVC) are prognostic parameters of cognitive impairment in COPD.[89] The majority of both national and international literature on effect of hypoxia on cognitive effects in patients with chronic lung disease, points to sub cortical type mild cognitive impairment with decline in attention, slower mental speed and compromised executive functions[90].

Lesions are found in frontal-subcortical pathways or in subcortical structures linking to the frontal lobes.[91,92] Attention and decision-making circuits involve pre-frontal cortex, thalamus, nucleus accumbens and heteromodal cortices (frontal, parietal and occipital) as well as paralimbic associated areas. The main neurotransmiter is acetylcholine, also serotoninergic and

dopaminergic pathways.

There is evidence of low acetylcholine concentration in the neocortex, hippocampus, striate nucleus and septal area, as well as dopamine in neocortex and hippocampus of mice submitted to the same conditions.[88] This is explained by the relative reduction in acetylcholine synthesis and other aminoacids due to lower carbohydrate oxidation in mild chronic hypoxia.[93-95] Decrease in sodium and potassium ion gradients which occur in chronic hypoxia conditions affects acetylcholine transport to neurons, lowering its uptake by the post-synaptic neuron.[96] It produces its effect through tissue hypoxia. Body tissues vary considerably in their vulnerability to hypoxia those with the greatest need of oxygen are the brain and the heart.

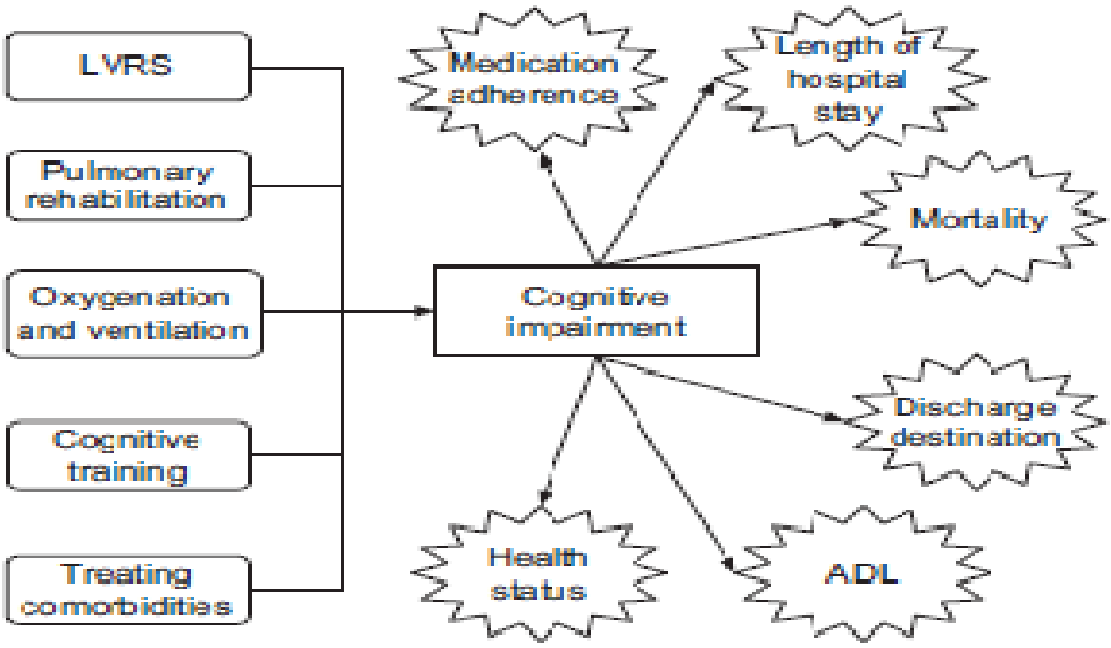
If PO_2 of the tissues fall below a critical level, aerobic metabolism ceases and anaerobic metabolism takes over and there is accumulation of lactic acid leading to metabolic acidosis. Mild hypoxemia produces few manifestations like slight impairment of mental functions. More pronounced hypoxemia produces personality changes, impaired judgement due to cognitive impairment. The manifestations of chronic hypoxia is insidious in onset and it is due to chronic lung disease[97]. Diagnosis is based on clinical observation and diagnostic measures of PO_2 levels. Arterial blood gas analysis gives the direct measure of O_2 content of the blood. Non invasive measurements of arterial oxygen

saturation of oxygen haemoglobin can be obtained by using Pulse Oximeter, which is an useful indicator of respiratory and circulatory status.

Arterial blood gases and pulse oximetry demonstrate resting or exertional hypoxemia. Arterial blood gases provide additional information about alveolar ventilation and acid-base status by measuring arterial P_{CO2} and pH. The change in pH with P_{CO2} is 0.08 units/10 mmHg acutely and 0.03 units/10 mmHg in the chronic state. Knowledge of the arterial pH therefore allows the classification of ventilatory failure, defined as P_{CO2}>45 mmHg, into acute or chronic conditions. The arterial blood gas is an important component of the evaluation of patients presenting with symptoms of an exacerbation. There is a subtle balance between central nervous system functioning and the pulmonary system.[89] Even small changes can have a major impact.[90] Hypoxia and hypercapnia in acute or chronic respiratory insufficiency can result in a myriad of neurological and neuropsychological signs and symptoms.

FIGURE – 6

POSSIBLE TREATMENTS AND OUTCOMES OF COGNITIVE IMPAIRMENT



PULMONARY REHABILITATION:

This refers to a treatment program that incorporates education for cognition and is necessary for cardiovascular conditioning. In COPD, pulmonary rehabilitation has been demonstrated to improve health-related quality of life, dyspnea, and exercise capacity. It has also been shown to reduce rates of hospitalization over a 6- to 12-month period.

Cognitive Evoked Potential in Animal studies:

In animal studies, odd ball paradigm was associated with a reinforcement either an electric shock (O'C onnor and Starr 1985), a juice reward (Paller et al) or a passive odd ball paradigm (Pinida et al 1988). Also the areas of the brain active during P_{300} were studied. In cats, activity was recorded in the thalamus, hippocampus, auditory cortex, and association cortex. In monkeys, activity has been recorded in the hippocampus. P_{300} has been demonstrated in tectum and retina of fish (Bullock et al). Many studies also evaluated the effects of lesions to different brain regions on P_{300}. Most of the study findings were negative. Even though there were lesions, P_{300} wave was still present.

In many studies (**Fix AJ** [98] **et al, Grant I et al** [14]**, Stuss D T et al**[84]**, Fioravanti M et al** [111] etc.,), cognitive impairment was found in COPD patients. They used a battery of neuropsychological tests to assess cognition. Recall was the important domain to be affected in COPD patients along with decline in

verbal memory. **Kozora et al[112] (1999)**, in his study found that the COPD patients performed significantly worse than the controls on verbal fluency tasks.

Incalzi RA et al[81] in his study, showed that 48.5% of patients with COPD had a specific pattern of cognitive deterioration characterized by a dramatic impairment in verbal memory tasks, and diffuse worsening of the other functions

Grant I, Heaton RK, McSweeny AJ, Adams KM, Timms RM[14], studied the Neuropsychological findings in hypoxemic COPD patients in 1982. They showed that mild hypoxemia may be associated with impairment in higher cerebral functioning including abstract reasoning, auditory and visual attention, verbal and non verbal learning, recall, reasoning, and motor skills".

Fix AJ, Golden CJ, Daughton D, KassI, Bell CW in 1982[98], showed that 64% of COPD patients included in their study scored less in MMSE, predominantly in recent memory, construction, attention, language, and orientation domains. Functional abnormalities were correlated with cognitive abnormalities".

Prigatano GP, Parsons O, Wright E, Levin DC, Hawryluk G. in 1983[99], found that cognitive domains such as speed, coordination, memory and learning, intelligence and attention were significantly

impaired in mild hypoxemic COPD patients which was correlated with partial pressures of oxygen".

Stuss DT, PeterkinI, Guzman DA, Guzman C, Troyer AK in 1997[84]. Studied the hypoxic effects on neurological and neuropsychological measures in Chronic obstructive pulmonary disease patients. This study states that there is significant relationship between blood arterial oxygen and carbon di oxide concentration and cognitive impairment.

Incalzi RA, Gemma A, Marra C, Capparella O, Fuso L, Carbonin P. (1997) in their study"[82], observed a decline of verbal memory which parallels that of the overall cognitive function in COPD patients and was found to be due to the impairment of both active recall and passive recognition of learned material".

Shim TS, Lee JH, Kim SY, Lim TH, Kim SJ, Kim DS, et al. in 2001,[100] states that cerebral metabolic abnormalities are observed in COPD patients which were detected by localized proton magnetic resonance spectroscopy.

Liesker JJ, Postma DS, Beukema RJ, ten Hacken NH, Vander MT, Riemersma RA, et al.[86]" in **2004** proved that COPD patients performed worse than the controls in speed, coordination, attention, and intelligence.

Reeves RR, Struve FA, Patrick G, Payne DK, Thirstrup LL[101] in their study on auditory and visual P_{300} cognitive evoked responses in patients with COPD and their relationship to the degree of pulmonary impairment found that auditory P_{300} latency significantly correlated with the FEV_1/FVC ratio (indicating that increasingly severe airflow impairment is associated with longer auditory P_{300} latencies. Progressive impairment of the auditory P_{300} evoked potential latency occurs with increasing severity of COPD. This impairment is present even in patients with mild COPD, suggesting some degree of accompanying cognitive decline early in the course of COPD with worsening as the disease progresses.

Hulya Ortapamuk, Seniha Naldoken in **2006 in their study**[102] **on** abnormalities in Brain perfusion in chronic obstructive pulmonary disease: comparison with cognitive impairment showed that the scores of verbal memory, delayed recall and vigilance were significantly lower in COPD patients. Hypoxemic patients showed more deterioration in cerebral perfusion and cognitive performance than non-hypoxemic patients.

Raffaele AntonelliIncalzi, Antonella Gemma, Camillo Marra, Rodolfo Muzzolon, Oliviero Capparella, and Pierugo Carbonin[104] in their study on Chronic Obstructive Pulmonary Disease: "An Original Model of Cognitive Decline", test scores revealed that 48.5% of COPD patients had a specific pattern of cognitive deterioration characterized by a remarkable verbal

memory impairment and visual attention was well-preserved with worsening of the other functions".

Aim and objectives

AIM AND OBJECTIVES

The aim of the present study is to assess cognition in stable COPD patients and to correlate cognition with their blood oxygen levels.

The objectives of the study were

1. To assess cognition in Stable COPD patients using MMSE, Stroop test (Neuropsychological tests) and the Cognitive Evoked Potential study (neurophysiological test).

2. To measure Arterial oxygen saturation (SpO_2) by using Pulse oximetry in Stable COPD patients.

3. To measure Partial pressure of Oxygen in Stable COPD patients by Arterial Blood gas analysis.

4. To correlate Blood Oxygen levels with Cognition in stable COPD patients.

5. To assess cognition and measure arterial oxygen saturation by Pulse Oximetry in age matched controls.

Materials & methods

MATERIALS AND METHODS

50 Stable COPD patients were selected on the basis of modified criteria defined in Global initiative for Chronic Obstructive Lung Disease (GOLD) guidelines.[20] They were clinically stable and belonged to mild and moderate category. After eliciting detailed history, general examination was done. Then, Clinical examination of Respiratory system was done. Arterial oxygen saturation was assessed with Pulse oximetry. Cognitive function was assessed using a screening test Mini Mental State Examination and a neuropsychological test Stroop test, Cognitive Evoked Potential Study and the results were recorded. Arterial blood gas analysis was done for patients.

50 age matched controls from a similar background were recruited. After eliciting history, general examination, clinical examination of Respiratory system, they were subjected to assess cognition and pulse oximetry was also done

STUDY DESIGN : Case control study

TYPE OF STUDY : Comparative study

PLACE OF STUDY:

Neurophysiology Lab, Department of Physiology,
Govt. Stanley Medical College.
Chennai-1.

DURATION OF STUDY : February 2014 to August 2014

ETHICAL CLEARANCE :

Obtained from Institutional Ethical Committee,
Govt. Stanley Medical College
Chennai- 1.

SUBJECT SELECTION:

STUDY GROUPS:

The study population consisted of 50 Stable COPD patients and 50 controls.

* CONTROL GROUP: The Control group were recruited from the College and Hospital workers and construction workers who volunteered for the study. They were age matched and had same educational qualification and socioeconomic background. Healthy men in the age group above 40 years, with normal spirometry findings. Arterial oxygen saturation was measured with pulse oximetry.

* STABLE COPD PATIENTS: The patients were recruited from the Pulmonology outpatient department at Govt. Stanley Medical College Hospital, Chennai 1. Stable COPD patients were identified and diagnosis was based on GOLD guidelines i.e., cough, sputum production, and difficulty in breathing with H/O exposure to smoking and spirometry results. They were above 40 years of age and in Stage-I & Stage-II-stable course of disease

Arterial Oxygen saturation was measured by Pulse oximetry. Arterial Blood Gas Analysis was done

EXCLUSION CRITERIA :

1. Auditory dysfunction,
2. Treatment H/O intake of any neurotoxic drug
3. H/O any traumatic lesion possibly affecting auditory functions or central nervous system
4. Cardiovascular or other systemic diseases
5. H/O any cognitive impairment/neurological deficit/neuropathy
6. Diabetes mellitus,
7. Chronic Alcoholism,
8. Chronic kidney disease and liver disease
9. Cystic fibrosis.
10. Any major medical illness at present or within three months.
11. Individuals with ear disease with hard of hearing
12. Vitamin deficiency

13. Individuals on psychotropic drug medications

14. H/O drug abuse

15. Persons with Overt Dementia (MMSE < 24)

16. Sleep disorders, Obstructive Sleep Apnoea (OSA),

All the subjects were explained about the nature and procedures involved in this study. The informed written consent from all the persons involved in this study was obtained.

HISTORY TAKING

The importance of demographic details is stressed while assessing cognition[21], smoking in pack years (20cigarettes /day for 1 year =1 pack year), occupation as an environmental factor was also entered.

In the stable COPD patients, history regarding various symptoms were also recorded.

CLINICAL EXAMINATION

Height and weight were taken and Body mass index (BMI) was calculated. Vitals like pulse, blood pressure, respiratory rate and temperature were recorded. Complete general and systemic examination was done . ENT examination was also done.

PULSE OXIMETRY

Blood oxygen saturation (SpO2) was evaluated for all subjects while they breathed room air in the supine position.

PULSE OXIMETRY PHOTOGRAPH-1

LUNG FUNCTION TESTS

They were performed using a dry spirometer device (Easy One). All the COPD patients were current smokers or ex-smokers. All were given proper instructions regarding the procedure. After inhaling salbutamol (Ventolin; GlaxoSmithKline; London, UK), spirometric indices were calculated using the best of the 3 good performances as recommended by American Thoracic Society as Classification of severity of airflow limitation is based on Post Bronchodilator FEV_1 as per GOLD Guidelines . The forced vital capacity (FVC), the forced expiratory volume in one second (FEV_1), and FEV_1/FVC ratio (FEV_1%) were obtained[22].

$FEV_1 \geq$ 80% predicted were classified as mild COPD;

$FEV_1 \leq$80% predicted were moderate COPD;

$FEV_1 \leq$50% predicted were severe COPD and

$FEV_1 \leq$30% predicted were very severe COPD.

Mild and moderate COPD patients were defined as mild-to-moderate COPD group, while severe and very severe COPD patients were defined as severe COPD group. Mild and Moderate COPD (Stable) patients were taken for the study.

ARTERIAL BLOOD GAS ANALYSIS (ABG):

Arterial blood gas analysis was performed by using cobas b 121 model instrument in the central laboratory only for the patients at rest in supine position. The syringe was washed with Heparin and after confirming the patency of radial and ulnar artery by doing Allens test. Radial artery pulsation was felt. The needle was inserted and radial arterial sample obtained during the mid-afternoon, after a 15min rest. Once the sample is ready it is taken and ABG analysis is done without delay. The arterial oxygen tension (PaO2), arterial carbon dioxide tension (PaCO2) and blood oxygen saturation (SaO2) was evaluated for all subjects. Samples were processed by a Cobas b 121 blood gas analyser (Ciba-Corning Ltd, Halstead, Essex, UK).

ARTERIAL BLOOD GAS ANALYSIS:PHOTOGRAPH-2

MINI MENTAL STATE EXAMINATION:

MMSE was done to assess cognition in all the subjects involved in this study .The following cognition domains were tested.

ORIENTATION

The individuals were asked simple questions to assess their orientation to person, place and time (year, month, day, date, time, country, town, district, hospital, floor).

Maximum score given was 10 points.

REGISTRATION

The individuals were told the names of 3 common objects e. g watch, fan, table and then asked to repeat them. One point was awarded for each correct answer.

Maximum score was 3 points.

ATTENTION AND CALCULATION

The individuals were asked to spell "WORLD" backwards - DLROW. One point was awarded to each correct answer.

Maximum score was 5 points.

RECALL

The individuals were asked to repeat the names of the three objects which were learnt earlier. One point was awarded to each correct answer.

Maximum score was 3 points.

LANGUAGE

i. CONFRONTATION: The individuals were shown 2 common objects and asked to name them. One point was awarded to each correct answer.

ii. The individuals were asked to repeat a phrase with no ifs, and or buts of 4 to 5 words. One point was awarded if repeated correctly.

iii. COMPREHENSION: The individuals were asked to follow a three staged command like “Take this paper in your right hand, fold it in half and put it on the floor”. One point was awarded to each stage if done correctly.

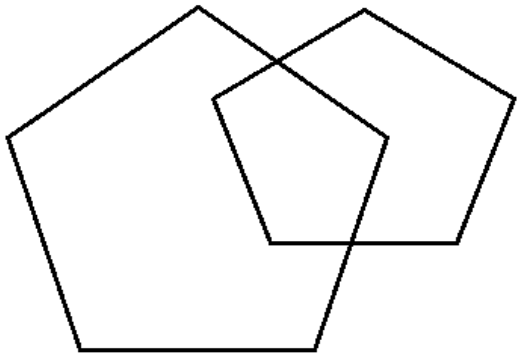
iv. The individuals were asked to read and obey a simple command like “close your eyes”. One point was awarded if the act was done correctly.

v. The individuals were asked to write a sentence of their own choice with Subject, Verb, Object). One point was awarded if written correctly.

Maximum score for language function was 8 points

COPYING:

CONSTRUCTION : The individuals were asked to copy a design (a pair of intersecting pentagons). One point was awarded if drawn correctly.



Maximum score of 1 point was awarded.

A total score of 30 points is possible. The score obtained by the individual was calculated and recorded.

STROOP TEST :

The test contains 176 boxes (11x16) of 4 names of colours (red, yellow, blue, green) randomly coloured and printed. While testing, the individual first reads the words in part 1 and names the colour in the second part. The subject is instructed to respond as fast as he can and accurately. The time taken for each parts and difference between the two are measured. This test requires about 15 minutes to complete. There was no time limit to complete a subtask. An interference measure was calculated by subtracting the average time needed

to complete the first and second task (Interference = Reading time-naming time). Valentin et al., 2005). The errors made during the test was not considered. Although many participants spontaneously corrected themselves when they noticed an error (which requires a certain amount of time, indirectly corrected for poor accuracy), this was not always the case. Number of errors made while reading and naming were also recorded.

COGNITIVE EVOKED POTENTIAL STUDY

Cognitive Evoked Potential study[23] was done for all the individuals in the study.

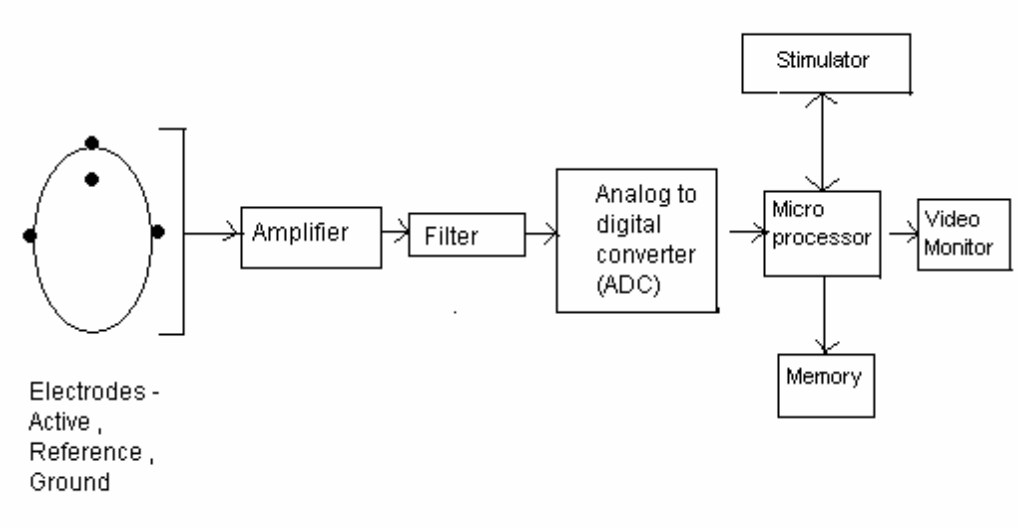
EQUIPMENT

The Cognitive Evoked Potential was recorded using a computerised recorder.

FIGURE- 7

COMPUTERISED RECORDER OF COGNITIVE EVOKED POTENTIAL

The machine used in this study was RMS EMG EP MARK II(Recorders and Medicare Systems Pvt. Ltd., Chandigarh. The machine includes a stimulator, recording electrodes, filter, amplifier, signal 90verage, electrical safety.



* ***Stimulator:***

The auditory stimulus in the form of clicks was given to both the ears via transducer placed in the head phone.

* ***Recording Electrodes*:**

Surface silver / silver chloride disc electrodes are used for recording the potentials.

* ***Filter*:**

Filter is a device, which selectively restricts a particular frequency domain. The filter band is the frequency range, which is transmitted through the filter. The frequency range which is rejected is known as stop band. Filtering is necessary for eliminating the noise and optimising the electro physiological recording. Filtering also brings out the characteristics of the wave form.

The low frequency filter removes the low frequency components and allows higher frequencies to pass the filter and are called high pass filters. Similarly the high frequency filter removes the higher frequencies and allows only the low frequency they are also known as low pass filters.

Filter setting for Cognitive evoked potential recording is as follows

Low pass filter 30 – 100 *Hz*

High pass filter 0.3 – 1 *Hz*

* ***Amplifiers*:**

ERPs are small relative to the spontaneous brain activity i.e., they have a low signal to noise ratio .Since the biological signals are very small, they need to be amplified. Cognitive evoked potentials are usually amplified 10,000 times.

* ***Signal Averager*:**

To increase the signal to noise ratio ERP averaging is done. To separate the cognitive evoked responses from the background EEG signal, averaging is done. This is based on the fact that the evoked potential electrical activity is time specific, whereas the random electrical activity is not time specific.

PREPARATION OF THE INDIVIDUALS

The individuals were instructed to have a shampoo bath on the day of recording and were advised not to use hair spray or oil. They were taken to a

silent sound proof room, and made to sit down comfortably in a chair with eyes closed.

Electrode Placement:

The electrode placement sites were cleaned with spirit and cotton. Electrode paste was used to reduce the impedance below 5 *kilo ohms.* The electrodes were placed according to International 10 – 20 system.

* Active surface recording electrode was placed on Vertex – Cz

* Two linked reference electrodes, one on each mastoid (A1 &A2) with a jumper electrode.

* Ground electrode was placed over the forehead.

RECORDING THE COGNITIVE EVOKED POTENTIAL

The cognitive evoked potential was recorded in a silent room using the standard auditory odd ball paradigm[23]. Random sequences of two distinguishable auditory clicks were delivered binaurally. It includes frequent stimuli (80%) of 1 KHz frequency and rare stimuli (20%) of 2 KHz frequency.

The individuals were asked to raise their finger on hearing the rare stimuli. The intensity of the stimuli was 60 db above hearing level. The stimuli were presented at the frequency of 1 per second, each lasting for 100 milli seconds. The responses were filtered with a band pass filter of 0.3 – 30 Hz; the responses were amplified 10,000 times and averaged for 40 responses. The

individuals were asked to fix their eyes on a particular point on the wall during recording to avoid electro oculographic artefacts.

The waves were then computed separately for rare and frequent stimuli. The latency of the N_{100}, and P_{300} waves, and P_{300} wave amplitude of the rare stimuli were noted down.

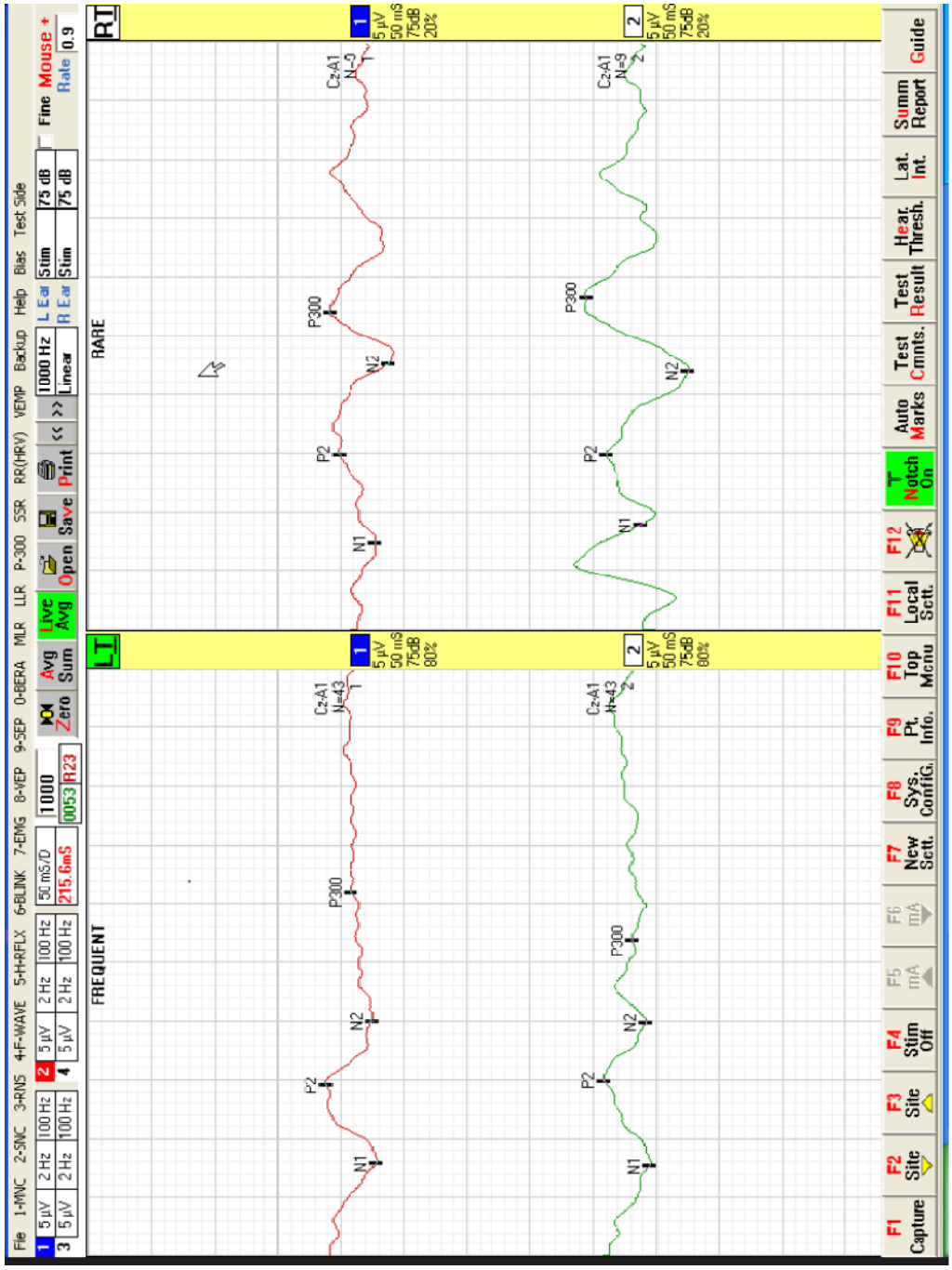
PHOTOGRAPH – 3

RECORDING OF CEP IN RECORDERS MEDICARE SYSTEMS (RMS EMG EP MARK – II MACHINE)

NEUROPHYSIOLOGY LAB,

DEPARTMENT OF PHYSIOLOGY

P_{300} WAVEFORM RECORDED



Results

STATISTICAL ANALYSIS

The collected data was analysed with SPSS 16.0 version. To describe about the data descriptive statistics frequency analysis, percentage analysis were used for categorical variables and the mean and S.D were used for continuous variables.

Independent t-test was used to find the significance difference between the bivariate samples in Independent groups (stable COPD group & Controls). The one way ANOVA with Tukey's Post-Hoc test was used for the multivariate analysis.

Pearson's Correlation was used to assess the relationship between the variables. Chi-Square test was used to find the significance in categorical data.

In all the above statistical tools, the probability value .05 is considered as significant level.Results were expressed as mean+/-standard deviation.

RESULTS

This study was to evaluate cognition in stable COPD patients by neuropsychological and neurophysiological methods and to correlate cognition with arterial oxygen saturation. To compare it with the normal controls.

THE CHARACTERISTICS OF CONTROL AND STABLE COPD PATIENTS

The characteristics of control and stable COPD patients are presented in Table 1.

A total of 50 stable COPD patients were recruited for the study. All were males and they were in the age group of 45-56yrs with a mean of 48 ±10 yrs of age and for the control group 49.46 ±7.24. There was no significant difference between the two groups with respect to age, height and educational status. They all had their education up to primary school. With regard to age, education, and socioeconomic status, the distribution of subjects both in stable COPD patients and control group was equal. The mean duration of illness in the COPD patients was found to be 8.980 ± 3.13 .Most of the COPD patients were labourers 28 number in stable COPD patients group and 23 number in the control group and they were exposed to dust. They were all smokers with a mean smoking pack years of 35.45±10.95 for the COPD patients and it is 8.23±5.89 for the control group.

The General and Central Nervous System Examination were found to be normal in both control and stable COPD patients.

TABLE 1

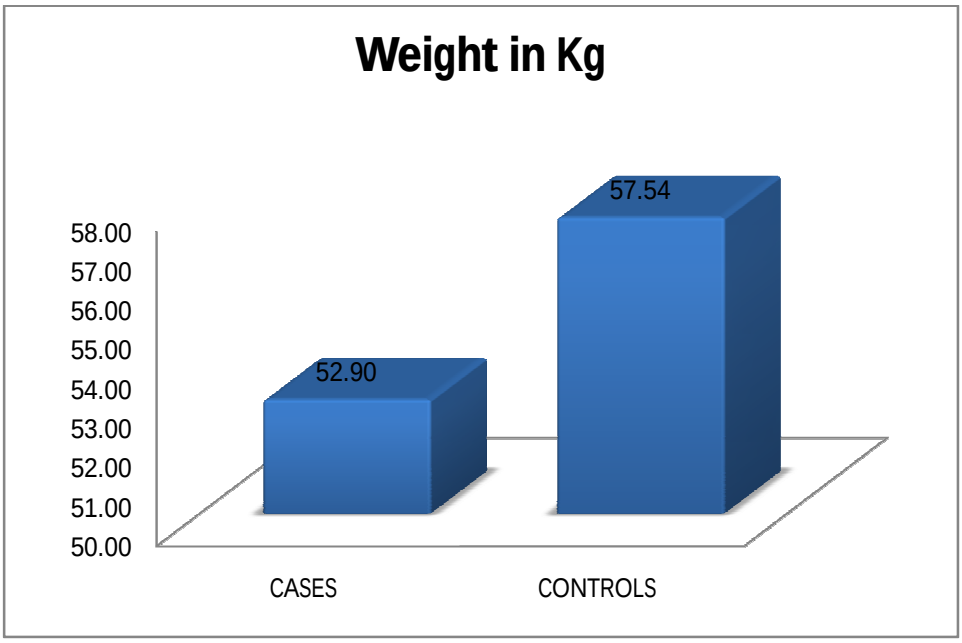
DEMOGRAPHIC CHARACTERISTICS (MEAN ± SD) OF THE STABLE COPD PATIENTS AND CONTROL GROUP

Variables	**Control group n= 50 Mean ± SD**	**Stable COPD patients group n= 50 Mean ± SD**
Age (years)	49.46±7.24	50.43±6.63
Duration of illness	NIL	8.980±3.13
Smoking in pack years	8.23±5.89	35.45±10.95
Height (meters)	1.60±0.09	1.59±0.07
Weight(kg)	57.54±11.09	52.90±8.84
BMI (kg/m^2)	22.49±3.99	20.77±3.03

The comparison of weight and BMI between the stable COPD patients and the control group is given in graphs 1&2.

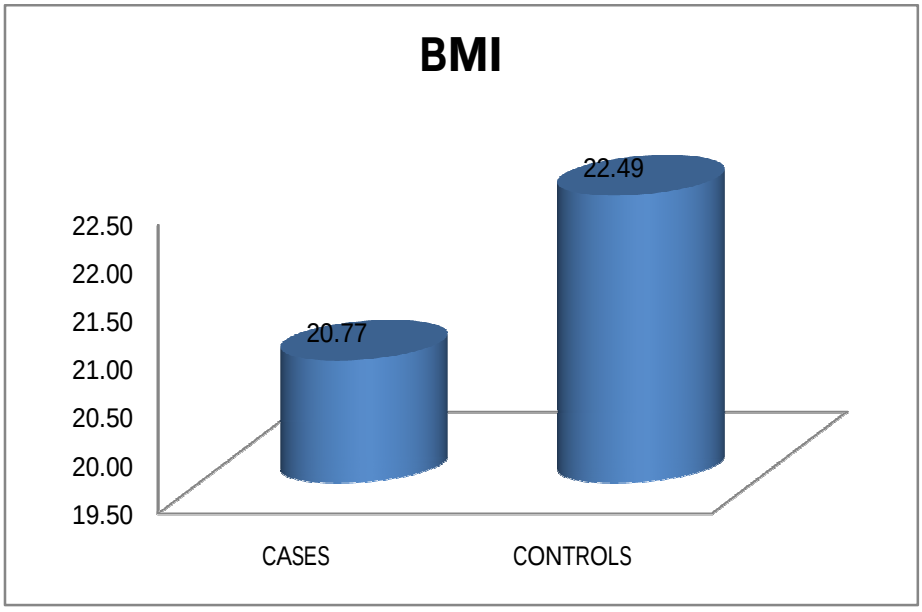
GRAPH- 1

COMPARISON OF (MEAN ± SD) values in WEIGHT BETWEEN THE STABLE COPD PATIENTS AND THE CONTROL GROUP



GRAPH-2

COMPARISON OF (MEAN ± SD) values in BMI BETWEEN THE STABLE COPD PATIENTS AND THE CONTROL GROUP



The Stable COPD patients they fall under the category of normal weight (18-22kg/m^2) according to new classification for Asian Indians BMI is 20.77±3.03 and for controls is 22.49±3.99 with p value .017 which is highly significant.

The comparison of Occupational status of the stable COPD patients and the control group is given in Table-2.

TABLE 2

COMPARISON OF OCCUPATIONAL STATUS OF THE CONTROL AND STABLE COPD PATIENTS

		STABLE COPD group	**CONTROLS**
OCCUPATION	Labourers	28	26
		54.9%	52.0%
	Others	22	24
		45.1%	48.0%

The Distribution of smoking Habit in the stable COPD patients and the control group is given in Table-3.

TABLE-3

DISTRIBUTION OF SMOKING HABITS IN THE STABLE COPD PATIENTS AND THE CONTROL GROUP

		STABLE COPD patients Group	**CONTROLS**
Smoking	Ex Smokers	17	1
		33.3%	2.0%
	Current Smokers	3O	25
		60.8%	50.0%
	Non Smokers	3	24
		5.9%	48.0%

In the STABLE COPD group, smokers were grouped as ex- smokers, current smokers and in the control group- ex-smokers current smokers.

The Comparison of Smoking pack years between the stable COPD patients and control group is presented in Table-4.

TABLE-4

COMPARISON OF SMOKING PACK YEARS BETWEEN THE STABLE COPD PATIENTS AND CONTROL GROUPS

		Stable COPD pts group	**Controls**
SMOKING TOBACCO	Non smokers	2	24
		3.9%	48.0%
	Less than 20 pack years	9	16
		19.6%	32.0%
	More than 20 pack years	39	10
		76.5%	20.0%

Smoking is calculated in pack years. In Stable COPD patients, smokers more than 20 pack years were 39(76.5%) and less than 20 pack years is 10(20%) where as in control it were 10(20%) more than 20 pack years, and less than 20 pack years 16(32%).

The Classification of mean values of FEV_1 based on the severity of COPD (GOLD GUIDELINES) is given in Table-5.

TABLE-5

STAGING OF COPD BASED ON MEAN VALUES OF FEV_1%(GOLD GUIDELINES)

STAGING	No of Stable COPD pts	FEV_1% MEAN±SD	p value
STAGE-I(Mild)	16	87.19±6.274	.000
STAGE-II(Moderate)	35	65.69±8.751	
Controls	50	88.02±11.315	

** Highly Sig. at $p < .01$ level

The mean values of FEV_1% of mild and moderate COPD patients were 87.19 ± 6.274 and 65.69 ± 8.751 respectively with a p value of.000 which is highly significant when compared to controls which were 88.02±11.315

PULMONARY FUNCTION TESTS

The comparison of mean values of FEV_1, FVC, FEV_1/FVC between the stable COPD patients and control groups is shown in Table-6 and graph-3

TABLE-6

COMPARISON OF FEV_1, FVC, FEV_1/FVC BETWEEN STABLE COPD PATIENTS AND CONTROLS

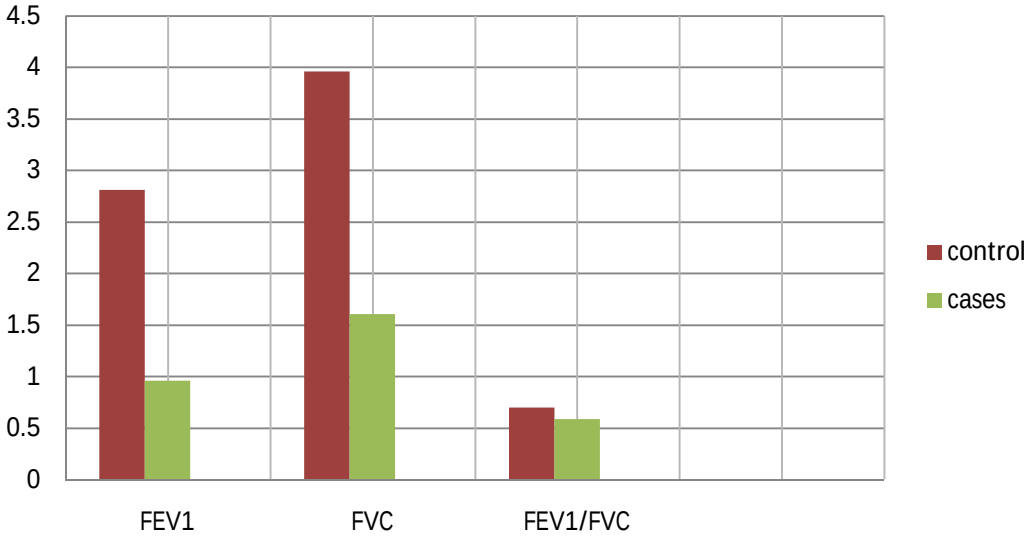
Variables	Control group n= 50 Mean ± SD	Stable COPD patients n= 50 Mean ± SD	p value
FEV_1	2.81 ± 0.21	0.96±0.39	0.000 **
FVC	3.96 ± 0.68	1.61±0.53	0.000 **
FEV_I/FVC	0.70 ±.09	0.59±0.11	0.000 **

** Highly Sig. at p< .01 level , * Sig. at p < .05 level & # No Sig.

The mean values of FEV_I, FVC and FEV_1/ FVC in the STABLE COPD patients were significantly lower (p value of.0001) when compared with the control group.

GRAPH- 3

COMPARISON OF FEV_1, FVC, FEV1/FVC BETWEEN STABLE COPD PATIENTS AND CONTROLS



NEUROPSYCHOLOGICAL TESTS

The Comparison of mean values of MMSE Score between the Stable COPD patients and the control group is given in Table - 7 & Graph-4

TABLE-7

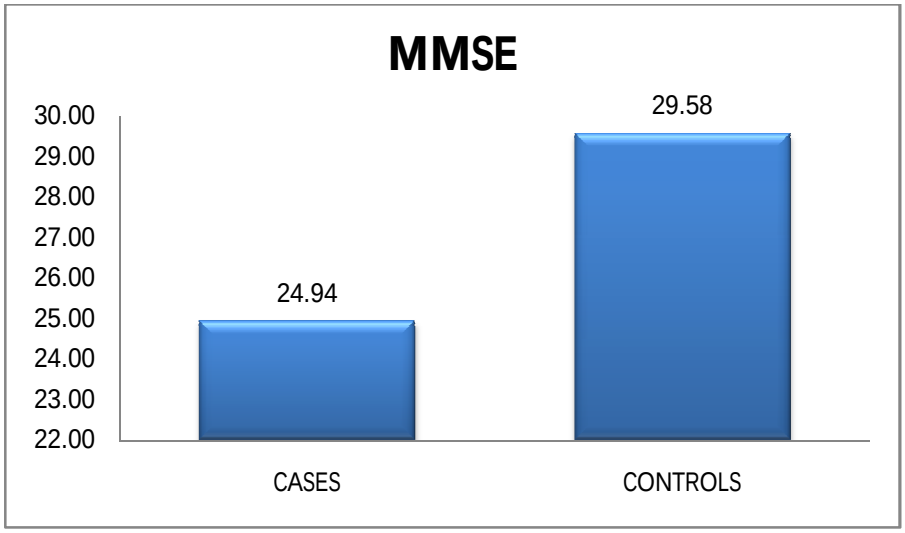
COMPARISON OF MEAN VALUES OF MMSE SCORE BETWEEN THE STABLE COPD PATIENTS AND THE CONTROL GROUP

Variable	Control group n= 50 Mean±SD	Stable COPD group n= 50 Mean ± SD	p value
MMSE	29.58±0.84	24.94±1.94	0.00 **

** Highly Sig. at p < .01 level , * Sig. at p < .05 level & # No Sig.

COMPARISON OF MEAN VALUES OF MMSE SCORE BETWEEN THE STABLE COPD AND THE CONTROL GROUP

GRAPH-4



A highly significant decrease in the MMSE score with a p value of 0.00 was observed in the Stable COPD patients when compared with the control group.

The comparison of mean values of Stroop test between the Stable COPD patients and control group is given in Table-8 and graph-5.

TABLE-8

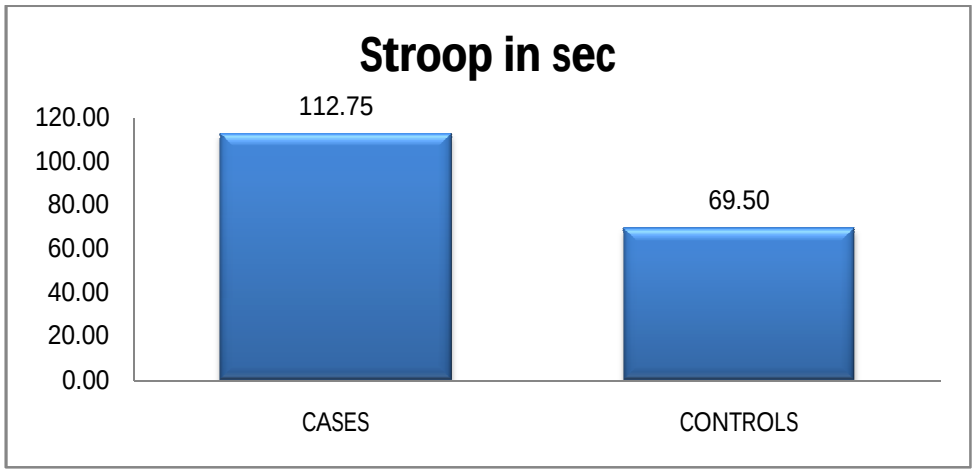
COMPARISON OF MEAN VALUES OF STROOP TEST BETWEEN THE STABLE COPD PATIENTS AND CONTROL GROUP

Variable	Control group n= 50 Mean±SD	Stable COPD patients n=50 Mean±SD	p value
STROOP IN SEC	69.50 ± 30.86	112.75 ± 38.68	0.00 **

** Highly Sig. at P < .01 level , * Sig. at P < .05 level & # No Sig

COMPARISON OF MEAN VALUES OF STROOP TEST BETWEEN STABLE COPD PATIENTS AND THE CONTROL GROUP

GRAPH-5



The mean value of Stroop test score is significantly (p value of .0001) increased when compared to the controls.

NEUROPHYSIOLOGICAL TEST

COGNITIVE EVOKED POTENTIAL STUDY: The comparison of the mean values of N_{100} wave latency, P_{300} wave latency, P_{300} wave amplitude between the control and Stable COPD patients are given in the Tables 10-12 & Graphs-7-9.

TABLE-9

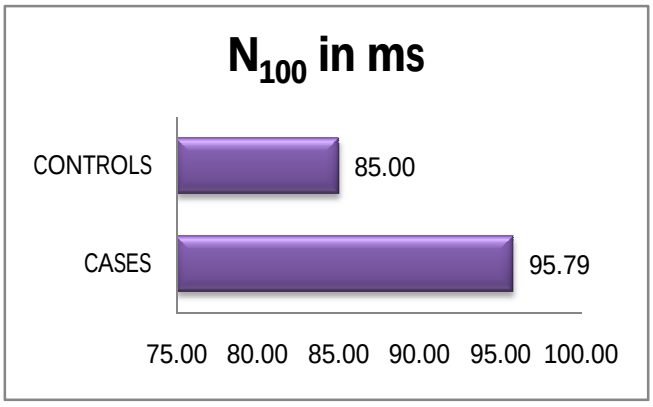
COMPARISON OF THE MEAN VALUES OF N_{100} WAVE LATENCY BETWEEN THE CONTROL AND THE STABLE COPD PATIENTS

Variables	Controls MEAN ± SD	Stable COPD patients MEAN ± SD	p value
Latency of N_{100} in ms	85±7.86	95.79±20.03	.001 **

** Highly Sig. at p < .01 level , * Sig. at p < .05 level & # No Sig.

COMPARISON OF THE MEAN VALUES OF N_{100} WAVE LATENCY (ms) IN THE STABLE COPD PATIENTS AND CONTROL GROUP

GRAPH-6



A highly significant increase in the N_{100} wave latency at Cz is observed in the stable COPD patients when compared to control group with a p value of .001.

TABLE-10

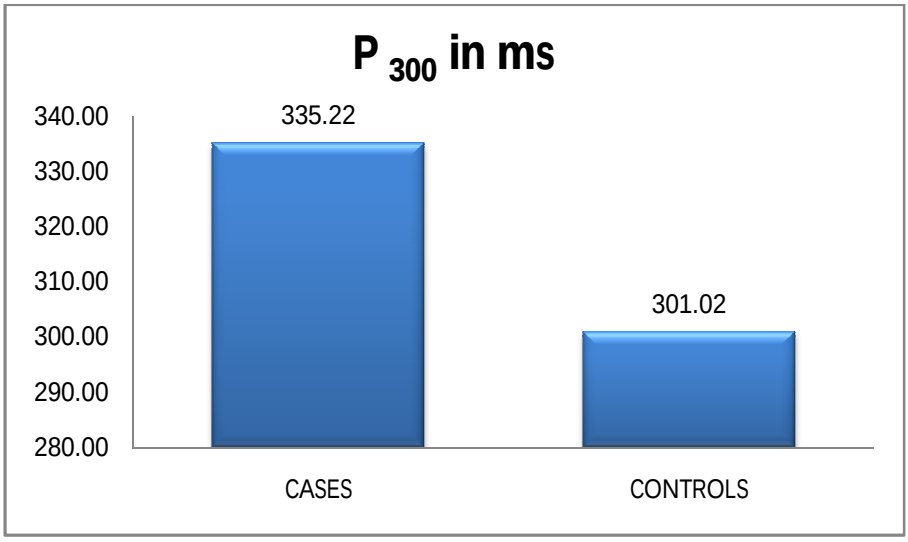
COMPARISON OF THE MEAN VALUES OF P_{300} WAVE LATENCY (ms) BETWEEN THE CONTROL AND THE STABLE COPD PATIENTS

Variables	Controls MEAN ± SD	stable COPD patients MEAN ± SD	p value
Latency of P_{300} (ms)	301.02 ± 9.38	335.22 ± 21.41	.0001 **

** Highly Sig. at p < .01 level , * Sig. at p < .05 level & # No Sig.

COMPARISON OF THE MEAN VALUES OF P_{300} WAVE LATENCY(ms) BETWEEN THE CONTROL AND THE STABLE COPD PATIENTS

GRAPH-7



A highly significant increase in the P_{300} wave latency at Cz in the Stable COPD patients group with a mean value of 335.22 ± 21.41 on comparing with the control group with a p value of .0001.

TABLE-11

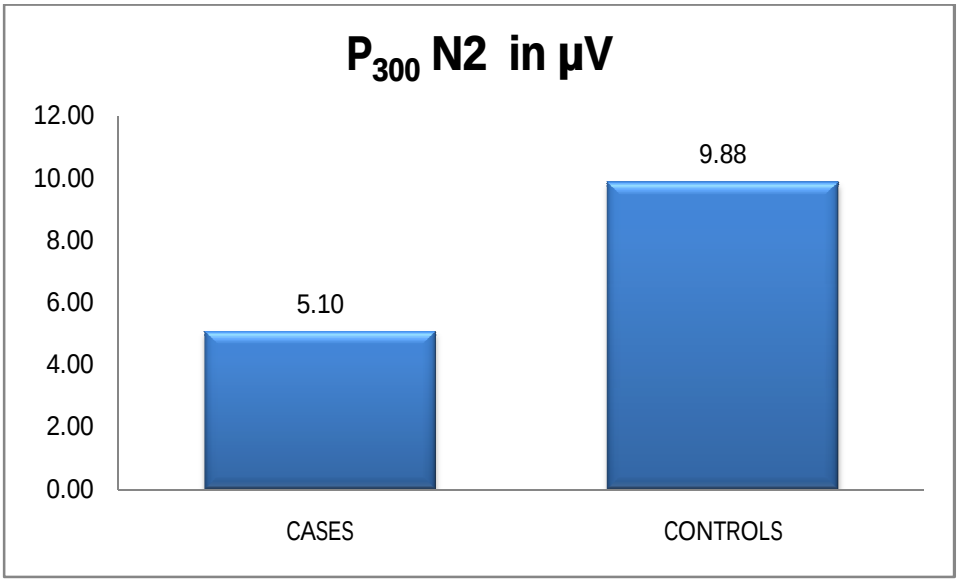
COMPARISON OF THE MEAN VALUES OF P_{300} WAVE AMPLITUDE BETWEEN THE CONTROL AND THE STABLE COPD PATIENTS

Variables	Controls MEAN ± SD	Stable COPD patients MEAN ± SD	p value
p_{300} amplitude in µv	9.88 ±13.02	5.10±1.45	0.010 **

The mean value of P_{300} wave amplitude at Cz in the Stable COPD patients is decreased significantly (p value of 0.010) when compared with the control group.

COMPARISON OF THE MEAN VALUES OF P_{300} WAVE AMPLITUDE BETWEEN THE CONTROL AND THE STABLE COPD PATIENTS

GRAPH-8



ARTERIAL OXYGEN SATURATION

Comparison of mean values of arterial oxygen saturation between Stable COPD patients and control group is given in Table-12 & Graph-9

TABLE-12

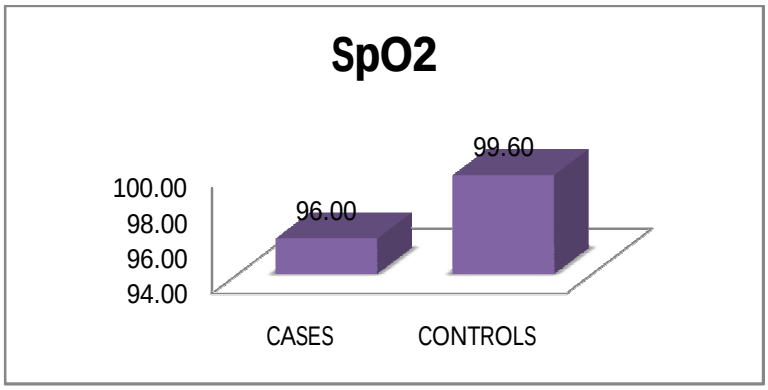
COMPARISON OF MEAN VALUES OF ARTERIAL OXYGEN SATURATION VALUES BETWEEN STABLE COPD PATIENTS AND CONTROL GROUP

Variable	Control group n= 50 Mean ± SD	Stable COPD pts group n= 50 Mean ± SD	p value
SpO2	99.60±0.70	96.00±2.35	0.00 **

** Highly Sig. at p < .01 level , * Sig. at p < .05 level & # No Sig.

COMPARISON OF MEAN VALUES OF ARTERIAL OXYGEN SATURATION VALUES BETWEEN STABLE COPD PATIENTS AND CONTROL GROUP

GRAPH-9



In the Stable COPD patients, the arterial oxygen saturation is significantly (p-value of .0001) lower when compared with the controls.

ARTERIAL OXYGEN SATURATION AND ARTERIAL OXYGEN TENSION

The mean values of Arterial oxygen saturation & Partial pressure of oxygen in Stable COPD patients is given in Table-13

TABLE-13

MEAN VALUES OF ARTERIAL OXYGEN SATURATION & PARTIAL PRESSURE OF OXYGEN IN STABLE COPD PATIENTS

Variable	Total No of Stable COPD patients	MEAN ± SD
SaO2	50	95.135±2.58
PaO2	50	77.671±15.13

CORRELATION BETWEEN ARTERIAL OXYGEN TENSION AND MMSE SCORE, STROOP TEST SCORE, N_{100} LATENCY, P_{300} LATENCY AND P_{300} AMPLITUDE

The correlation between Arterial oxygen tension and MMSE, Stroop test, N_{100} latency, P_{300} latency and P_{300} amplitude is given in Table 14 - 17

TABLE-14

CORRELATION BETWEEN ARTERIAL OXYGEN TENSION AND MMSE IN STABLE COPD PATIENTS :

	Correlation coefficient and pvalue	**Interpretation**
Correlation between arterial oxygen tension & MMSE score in Stable COPD patients	r = -0.124 p = 0.388	Weak negative correlation Not significant

CORRELATION BETWEEN ARTERIAL OXYGEN TENSION AND STROOP TEST IN STABLE COPD PATIENTS :

TABLE-15

	Correlation coefficient and p value	**Interpretation**
Correlation between arterial oxygen tension & Stroop test in Stable COPD patients	r = .067 p = .640	Weak positive correlation Not significant

TABLE-16

CORRELATION BETWEEN ARTERIAL OXYGEN TENSION AND P_{300} LATENCY IN(m sec) IN STABLE COPD PATIENTS :

	Correlation coefficient and p value	**Interpretation**
Correlation between arterial oxygen tension & P_{300} latency in ms in Stable COPD patients	r = .200 p = .159	Weak positive correlation Not significant

TABLE-17

CORRELATION BETWEEN ARTERIAL OXYGEN TENSION AND P_{300} AMPLITUDE IN(µV) IN COPD PATIENTS :

	Correlation coefficient and p value	**Interpretation**
Correlation between arterial oxygen tension & P_{300} Amplitude in µV in Stable COPD patients	r =.270 p = .55	Positive correlation Not significant

Discussion

DISCUSSION

All stable COPD patients included in this study fulfilled GOLD CRITERIA for assessing the severity of COPD. They were all symptomatic with H/o difficulty in breathing, productive cough, and fatigue.

Stable patients included in this study were on regular treatment for 6 or more months with no history of exacerbations.

CHARACTERISTICS OF STUDY SUBJECTS :

The mean age of stable COPD patients included in the study was 48 ± 10 yrs of age ranging from 38 years to 58 years. In a study by **Hulya Ortapamuk et al**[103], the study group were within the range of 45 - 65 years, **Orth et al** [87], included the age group more than 55 years, Jing Li et al studied age group more than 65 years and in a study by **Prem Parkash Gupta et al**[104], the subjects were in the age group more than 40 years.

Due to the high prevalence of COPD among males, the present study included only male individuals.

The mean value of duration of illness in COPD patients was 8.980 ± 3.13 yrs. The mean value of smoking in pack years in COPD patients was 35.45±10.95, which was significantly more when compared to the controls. Occupational exposure to dust was found to increase the severity of disease

process which in turn influences the development of cognitive impairment in COPD patients. Above results were consistent with the study done by **Prem Parkash Gupta et al**[104].

Among the COPD patients, 76.5 % had > 20 smoking pack years, 19.6 % had < 20 smoking pack years and 3.9 % were non smokers. This shows that smoking is an important risk factor for COPD. Smoking has a direct neurotoxic effect. It increases carbon monoxide level causing cerebral hypoxia which plays an important role in the pathogenesis of COPD and cognitive dysfunction as suggested by **Antonella De Carolis et al** in 2011 and he found out that processing speed and verbal memory were affected in his study group due to smoking.

The mean value of body mass index was 20.77 kg/m^2 in COPD patients which was significantly lower (22.49 kg/m^2) when compared to controls. In a study by **Gupta et al** [105], malnutrition was present in 83% of COPD patients. It is due to the end result of an imbalance between energy intake and consumption by the body. Impairment of leptin regulation and inadequate intake due to difficulty in breathing leads to decreased BMI. [106]

Staging of COPD patients was done based on GOLD CRITERIA for COPD severity using FEV_1% values. The number of patients in stage I (mild) were 16 with the mean value of FEV_1% as 87.19 ± 6.27 and 35 patients were in stage II (moderate) with a mean value of FEV_1% as 65.69 ± 8.75. Thus the present study included mild and moderate stable COPD patients. Similarly, in a

study done by **Jing Li et al and Gupta et al**, COPD patients belonging to mild and moderate stages were included unlike in studies done by **Fix et al, Grant et al and Ohrui et al**, who included only severe group .

The present study was carried out to assess the cognitive status and to record the early changes that occur in the neuronal cells induced by hypoxia. Hence COPD patients who were exposed to hypoxic episodes during their daily activities, sleep and during exertion were included in this study. Hypoxic episodes were also seen during acute exacerbation of the illness, which is very common and not reported often in COPD patients with cognitive impairment due to loss of self assessment of illness.

NEUROPSYCHOLOGICAL TESTS: Many studies have assessed cognition by a battery of neuropsychological tests. Cognition domains are multiple and there are a number of specific tests to assess each domain. Neuropsychological testing requires time and a trained psychiatrist to perform and to interpret the findings.

MMSE SCORE :

In this study the mean values of MMSE score in COPD patients was 24.94±1.94 which was significantly lower than the controls. Among the cognition domains, verbal memory and motor speed were significantly impaired in COPD patients. These observations are similar to the study done by **Prem Parkash Gupta et al** [104]**,** In a study by **Grant**[14] **et al and Prigatano**[99] et al in

1987, poor MMSE scores in COPD patients was related to moderate and severe hypoxemia.

Reduced MMSE scores observed in COPD patients in the present study, suggests cognitive dysfunction in them.

Cognitive impairment was observed in COPD patients in many studies like **Fix AJ**[98] **et al, Grant I et al** [14]**, Stuss D T et al** [84]**, Fioravanti M et al**[111]. Recall was the important domain to be affected in COPD patients along with decline of verbal memory and this holds true in the present study where most of the COPD subjects were not able to recall and copy a design. **Allen and co-workers**[107-110] had confirmed that low performance on the MMSE and its intersected pentagon part are significantly linked to worse performance in the ability to learn and retain inhaler techniques and it is consistent with our study.

STROOP TEST SCORES:

In this study, the subjects showed poor performance in naming than reading and the interference score was significantly affected with a mean value of 112.75±38.68 sec. In a study by **Fix A J et al in** 1982, the neuropsychological tests which included stroop colour and word test scores were significantly related to partial pressure of arterial oxygen (PaO2), and to degree of pulmonary impairment. The cognitive deficits were real, but small. **Igor Grant, MD et al**[14] in their study in 1999, found that higher cognitive

functions (abstracting ability, complex perceptual-motor integration) most severely affected but half the percentage of patients showed decrements in motor speed, strength, and coordination. **Kozora et al[112] in 1999**, showed that COPD patients performed significantly worse than the controls on verbal fluency tasks. **Incalzi R A et al**[81] in his study, observed that 48.5% of COPD patients had a specific pattern of cognitive deterioration which was characterized by a dramatic impairment in verbal memory tasks, and diffuse worsening of the other function. Above findings are consistent with our study. Abnormal stroop test scores observed in the COPD patients, indicates impaired cognitive flexibility.

COGNITIVE EVOKED POTENTIAL STUDY

In the present study, the COPD patients had significant prolongation of N_{100} and P_{300} wave latencies and decreased P_{300} wave amplitude, when compared to the control group.

In our study, there was significant prolongation of N_{100} latency with a mean value of 95.79±20.03 when compared to controls. The N_{100} wave is the largest component and it is considered to reflect initial sensory processing and early selective attention capacities during stimulus processing causing arousal and attention (Strik et al, 1992).

The mean value of P_{300} latency in COPD patients was 335.22 ± 21.41 which was significantly increased when compared to controls. Similar results were observed in studies done by **A.R AL Tahan**, et al, **Kirkil G et al** [115] and **Gupta PP et al.**

P_{300} test can be considered as a potential objective marker of cognitive impairment. The P_{300} is used as a surrogate marker of information processing, attention and intellect memory. During acute exacerbation of COPD Patients were reported to have impaired attention, information processing and memory.

The mean value of P_{300} amplitude in COPD patients was 5.10 ± 1.45. This was significantly lower when compared to controls. Similarly decrease in p_{300} amplitude was observed in studies by **A.R AL Tahan** et al., and **Gupta PP et al.,**

P_{300} amplitude depends on the selective attention of the individual. It is greater with attentive individual, and with better motivation and task priority.

The significantly prolonged N_{100} wave latency, P_{300} latency and decreased P_{300} amplitude in the COPD group implies impaired attention.

ARTERIAL OXYGEN SATURATION AND ARTERIAL OXYGEN TENSION

In our study, the men arterial oxygen saturation in COPD patients was 96.00 ± 2.35 % when compared to controls. The mean arterial oxygen tension (PaO2) in COPD patients was found to be 77.67 ± 15.13 mm Hg. However it was in the normal range. The PaO2 usually remains near normal until the FEV1 is decreased to nearly 50% of predicted and even much lower FEV1 values can be associated with a normal PaO_2[32]. Oxygen desaturation may occur during day

to day activities leading to demyelination of cerebral cortex in COPD patients. Reduced SpO2 is due to low V/Q ratio leading to physiologic shunt and high V/Q ratio leading to increased physiologic dead space in COPD subjects and it is a risk factor for COPD exacerbation (**Faganello M M et al**[114], 2010). **Orth et al**[87] in 2006, observed a significant association between SpO2 and COPD severity. **Rabe KF et al**[113] (2007), observed that as alveolar hypoxia progresses to hypoxemia, the severity of COPD increases.

National Emphysema Treatment trial by **Martinez FJ et al** in 2006[119] and UPLIFT study done by **Tashkin DP et al** in 2008, revealed that COPD patients were hypoxic and they required Oxygen therapy. This proves that hypoxemia is the major factor causing cognitive impairment. **Liesker JJ e**t al[86]**,** observed that even non-hypoxemic patients with COPD showed significant impairment in cognitive performance and this goes hand in hand with the present study.

CORRELATION OF VARIABLES

There was no significant correlation between arterial oxygen tension and MMSE, Stroop test, and P_{300} latency. However there was a positive correlation between arterial oxygen tension and P_{300} amplitude but it was not statistically significant. The reasons for weak correlation could be attributed to minimum sample size covered in the study and only few percentage of COPD patients fall beyond the mean ± 3' SD value range of normal subjects with respect to all variables assessed in the study.

Kim V Benidict JO et al (2008) stated that," hypoxemia leads to poor cognitive function, poor quality of life, and finally increased risk of COPD exacerbation and death". In a study by **Fix et al, decreased** PaO_2 correlated with attention, processing speed, and motor function. **Stuss et al** observed memory changes in relation to PaO_2. **Allen SC, Jain M, Ragab S, et al in 2003**[108], showed that in COPD patients, SpO2 was significantly decreased. SpO2 and PaO2 were significantly correlated with pulmonary involvement. They suggested that intact cognition is essential for the use of inhaler by the COPD patients.

Finally, early cessation of smoking in COPD patients will help to reduce the comorbidities like cognitive impairment. Cognitive impairment is seen in 61% of moderately hypoxemic and 27% of mildly hypoxemic patients in the present study. Treatments should be designed to improve brain oxygenation in order to prevent the progression of cognitive dysfunction in COPD patients.

Supplemental oxygen therapy (**Kropp et al in 1973**[114],**Heaton et al in 1983**) demonstrated slight improvement in motor speed and strength, exercise training. It has reduced post exercise sympathetic hyper arousal, improved neurotransmitter regulation and oxygen carrying capacity of the blood. This improved verbal fluency, processing and thus frontal lobe executive functions (**Dustman et al in 1984**)[118]. Rehabilitation (**Emery et al., 1998, 2001, 2003**[117]), and Lung volume reduction surgery improved psychomotor skills and verbal naming with improvement in quality of life (**Kozora et al**., **2005**[112]).

Thus it is clear that intact cognition is essential for the COPD patients so that the treatment can be planned to prevent hypoxic episodes which is the major cause of cognitive impairment and to delay the progression of illness by Pulmonary Rehabilitation.

Conclusion

CONCLUSION

The following conclusions have been derived from the present study,

It is proved that there is definite cognitive impairment in Stable COPD patients when compared with the controls. The Stable COPD patients were in normal, mild and moderate stages of hypoxia as indicated by Partial Pressure of oxygen. Inspite of having near normal oxygen levels, there is cognitive impairment as assessed by MMSE, Stroop colour word test and the Cognitive evoked potential study.

In Stable COPD Patients, the Central nervous system involvement is clearly proved by the non-invasive cognitive assessment tests. In future, these tests may be recommended in all stable COPD patients as a routine investigation

1) to detect early impairment of cognition,

2) to plan our management to improve cognition and

3) to delay the progression of illness by Pulmonary Rehabilitation which will improve the quality of life in COPD patients.

Summary

SUMMARY

This cross sectional comparative study was done in the Neurophysiology Laboratory, Department of Physiology, Govt. Stanley Medical College, Chennai-1 to assess cognition by MMSE, Stroop test and Cognitive evoked potential study and to correlate with arterial oxygen tension in Stable COPD patients.

The study included 50 Stable COPD patients and 50 controls.

MMSE score was significantly lower in Stable COPD patients. Stroop test score was significantly altered in Stable COPD patients when compared with the controls. The Latency of N_{100} and P_{300} wave of cognitive evoked potential was prolonged and P_{300} amplitude was decreased.

Arterial oxygen saturation and tension was found to be significantly decreased in patients. Though there was a positive correlation between arterial oxygen tension and P_{300} amplitude in COPD patients, it was not statistically significant.

The above results show that hypoxia can be attributed to impairment in cognition. MMSE can be used as a screening tool, and Stroop test to assess cognitive flexibility. CEP study can be used to identify early cognitive impairment. Further studies are required to assess cognition after cognitive training and pulmonary rehabilitation to know whether cognitive impairment is

reversible or it stops its progression which would be helpful in the prompt management of the condition.

The above results were discussed and compared with other published studies.

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Annexure

PROFORMA

Proforma for the study subject : Date:

1. S. no :

2. I.D (given by investigator): Address &Contact No.

3. Name :

4. Age :

5. Gender : Religion:

6. Pulmonology Dept.No. /Master Health checkup no.:

7. Occupation : Not working/Housewife/labourer- what type of work: duration: /Professional/others(specify):

8. Family History of COPD,TB: Parents / Siblings

9. Educational Qualification : uneducated/school /College/ Professional :

10. Per Capita Income:

Number of family members :

Net family income:

11. Duration of illness :

12. Social Habits :

	Past/present/ Newer	Beedi/Cigarette/Brand/ quantity/Pack years	Duration
1. Smoking	/day		
2. Alcohol			
3. Tobacco			
4. Any other substance abuse			

13. Past history:

14. Treatment history: Increased need for drugs: oral IM/IV Inhaler Nebulizer Number of hospitalisations: :Duration of stay: ICU/Mechanical ventilatory support

15. Associated Co morbidities:

Clinical Details:

16. Symptoms : Duration:

*Cough: dry or productive

*Difficulty in breathing :

*Fever:

* Chest pain:

*Loss of weight:

* Loss of appetite:

Fatigue

Sleep disturbance:

Palpitation

Activity limitation

*any other relevant complaints:

17. On Examination :

* Height :

* Weight :

* Built :

* Nourishment

* B M I :

Respiratory rate : Pulse: Blood Pressure :

Clinical Examination of Respiratory System:

18. Investigations : Urine Examination:

Blood Investigations: RBC count: WBC count: Hb%: PCV:

Blood Glucose: Serum Electrolytes:

Pulse Oximetry: Blood arterial gas analysis: pH

X-ray chest PA view PO_2

ECG in all leads PCO_2

Spirometry: FVC: HCO_3

FEV1:

FEV1%

FEV1/FVC%:

PEFR :

Clinical Diagnosis :

19. MMSE Scale:

20. Stroop test:

21. Event Evoked Potential Response:

Variables		
Latency		
Amplitude		

நோயாளி தகவல் தாள்

நாள்பட்ட நுரையீரல் அடைப்பு நோயுடைய நோயாளிகளின் எண்ணங்களால் நரம்புகளில் தூண்டப்படும் மின் அதிர்வுகள் மற்றும் தமனியில் ஆக்ஸிஜன் வாயுவின் அளவையும் ஆராய்தல்.

நோயாளிகளுக்கான தகவல்:

ஆராய்ச்சியின் நோக்கமும், ஆதாரங்களும் உங்கள் பங்கேற்பு திட்டமிடப்பட்டுள்ள இந்த ஆராய்ச்சி ஆய்வின் நோக்கம் இது ஆற்றல் மிக்கதாகவும் மற்றும் பாதுகாப்பாகவும் இருப்பதாக அறியப்படுகிறது. இந்த ஆய்வின் மூலம் பெறப்படும் அறிவானது உங்களைப் போன்று பல்லாயிரக்கணக்கான நோயாளிகளுக்கு நன்மை தருவதாக அமையும்.

உண்டாகக் கூடிய இடர்கள்:

அனைத்து புதிய முறைகளிலும் இருப்பது போலவே இந்த முறையிலும் சில எதிர்பாராத இடர்களை சம்பந்தப்பட்டுள்ளன.

ஆய்வு நடைமுறைகள்:

இந்த ஆய்வில் நீங்கள் புறநோயாளியாகவோ இருப்பீர்கள். உங்கள் எண்ணங்களால் நரம்புகளில் தூண்டப்படும் மின் அதிர்வுகள் மற்றும் ஆக்ஸிஜன் வாயுவின் அளவும் உட்கார்ந்த நிலையில் அளக்கப்படும்.

அந்தரங்கத் தன்மை:

உங்கள் மருத்துவமனை பதிவேடுகள் மிகவும் அந்தரங்கமாக வைத்துக் கொள்ளப்படும் மற்றும் பிறமருத்துவர்கள், விஞ்ஞானிகள் இந்த ஆய்வின் தணிக்கையாளர்கள் அல்லது ஆராய்ச்சி ஆதரவாளர்களின் பிரதிநிதிகள் ஆகியோரிடம் அவை வெளிப்படுத்தப்படும். இந்த ஆய்வின் முடிவுகள் அறிவியல் பத்திரிக்கைகளில் பிரசுரிக்கப்படலாம். ஆனால் பெயரை வெளியிடுவது மூலம் நீங்கள் அடையாளம் காட்டப்பட மாட்டீர்கள்.

ஆய்வில் பங்கேற்கும் நோயாளியின் கடமை பொறுப்புகள்:

உங்களை கவனித்துக் கொள்ளும் மருத்துவருடன் நீங்கள் முழுமையாக ஒத்துழைக்க வேண்டும் என்று உங்களை கேட்டுக் கொள்கிறேன். சிகிச்சையளிக்கும் மருத்துவர் கொடுக்கும் அறிவுரைகளை பின்பற்ற வேண்டுமென்றும் என்னென்ன செய்ய வேண்டும் எனனென்ன செய்யக் கூடாது என்றும் உங்களிடம் கூறப்பட்டுள்ளவற்றிலிருந்தும் சற்றும் விலக்கூடாது என்றும் நீங்கள் எதிர்பார்க்கப்படுகிறீர்கள்..

ஆய்வில் உங்கள் பங்கேற்பு மற்றும் உங்கள் உரிமைகள்:

இந்த ஆய்வில் உங்கள் பங்கேற்பு தன்னிச்சையான மற்றும் காரணங்கள் எதையும் கூறாமலேயே நீங்கள் இந்த ஆய்விலிருந்து எந்த ஒரு நேரத்திலும் விலகிக் கொள்ளலாம். ஆய்வில் உங்கள் பங்கேற்பை மறுப்பது போன்ற எந்தவித அபராதமும் விதிக்கப்படாது. உங்களை கவனித்துக் கொள்ளும் மருத்துவருடன் முழுமையாக ஒத்துழைக்க நீங்கள் சம்மதிக்க வேண்டும். வேறு ஏதேனும் கேள்விகள், பிரச்சனைகள் பற்றி நீங்கள் கேட்க விரும்பினால் கீழ்க்கண்ட நபரை தொடர்பு கொள்ளவும்.

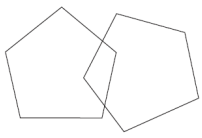
(ஆய்வில் பங்கேற்பவர் கையொப்பம் அல்லது பெருவிரல் பதிவு)

ஒப்புதல் படிவம்

திரு / திருமதி / செல்வன் / செல்வி ..... ஆகிய நான் _____ பட்ட மேற்படிப்பு மாணவர். உடல் இயங்கியல் துறை, ஸ்டான்லி மருத்துவக் கல்லூரி நடத்தும் ஆராய்ச்சியில் யாருடைய வற்புறுத்தலும் இன்றி என்னுடைய முழு சம்மதத்துடன் பங்கேற்க சம்மதம் தெரிவிக்கிறேன். இந்த ஆராய்ச்சி என்னுடைய எண்ணங்களால் நரம்புகளில் தூண்டப்படும் மின் அதிர்வுகளை அறிந்து கொள்ள உதவியாக இருக்கும் என்பதை நான் அறிந்து கொண்டேன். இந்த ஆராய்ச்சியில் எந்தவித மருந்துகளோ, ஊசிகளோ அளிக்கப்படவில்லை. இந்த ஆராய்ச்சியின் செயல்பாடுகளை ஆராய்ச்சியாளர் மூலம் அறிந்து கொண்டேன். நான் இந்த ஆராய்ச்சியில் இருந்து எந்தவித முன்னறிவிப்புமின்றி விலகிக் கொள்ள எனக்கு உரிமை உண்டு. இந்த ஆராய்ச்சியின் ஏடுகள் ரகசியமாக வைக்கப்படும் என்பதை நான் அறிவேன்.

கையெழுத்து

STANDARDIZED MINI-MENTAL STATE EXAMINATION(SMMSE)

QUESTION	TIME ALLOWED	SCORE
a. ***What year is this?***	10 seconds	/ 1
b. ***Which season is this?***	10 seconds	/ 1
c. ***What month is this?***	10 seconds	/ 1
d. ***What is today's date?***	10 seconds	/ 1
e. ***What day of the week is this?***	10 seconds	/ 1
a. ***What country are we in?***	10 seconds	/ 1
b. ***What province are we in?***	10 seconds	/ 1
c. ***What city/town are we in?***	10 seconds	/ 1
d. ***IN HOME – What is the street address of this house?*** ***IN FACILITY – What is the name of this building?***	10 seconds	/ 1
e. ***IN HOME – What room are we in? IN FACILITY – What floor are we on?***	10 seconds	/ 1
SAY: ***I am going to name three objects. When I am finished, I want you to repeat them. Remember what they are because I am going to ask you to name them again in a few minutes.*** Say the following words slowly at 1-second intervals - **ball/ car/ man**	20 seconds	/ 3
Spell the word WORLD. Now spell it backwards.	30 seconds	/ 5
Now what were the three objects I asked you to remember?	10 seconds	/ 3
SHOW wristwatch. **ASK:** ***What is this called?***	10 seconds	/ 1
SHOW pencil. **ASK**: ***What is this called?***	10 seconds	/ 1
SAY: ***I would like you to repeat this phrase after me: No ifs, ands or buts.***	10 seconds	/ 1
SAY: ***Read the words on the page and then do what it says.*** Then hand the person the sheet with CLOSE YOUR EYES on it. If the subject reads and does not close their eyes, repeat up to three times. Score only if subject closes eyes	10 seconds	/ 1
HAND the person a pencil and paper. **SAY:** ***Write any complete sentence on that piece of paper.*** (Note: The sentence must make sense. Ignore spelling errors)	30 seconds	/ 1
PLACE design, eraser and pencil in front of the person. **SAY**: ***Copy this design please.***  Allow multiple tries. Wait until person is finished and hands it back. Score only for correctly copied diagram with a 4-sided figure between two 5-sided figures.	1 minute	/ 1
ASK the person if he is right or left-handed. Take a piece of paper and hold it up in front of the person. **SAY**: ***Take this paper in your right/left hand*** (whichever is non- dominant), ***fold the paper in half once with both hands and put the paper down on the floor*** . Score 1 point for each instruction executed correctly. Takes paper correctly in hand Folds it in half Puts it on the floor	30 seconds	/ 1 / 1
TOTAL TEST SCORE		**/30**

சிவப்பு	மஞ்சள்	நீலம்	பச்சை	மஞ்சள்	நீலம்	பச்சை	நீலம்	சிவப்பு	நீலம்	மஞ்சள்
நீலம்	மஞ்சள்	பச்சை	மஞ்சள்	சிவப்பு	மஞ்சள்	சிவப்பு	நீலம்	பச்சை	சிவப்பு	பச்சை
மஞ்சள்	பச்சை	நீலம்	சிவப்பு	மஞ்சள்	நீலம்	மஞ்சள்	சிவப்பு	மஞ்சள்	பச்சை	சிவப்பு
பச்சை	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	மஞ்சள்	மஞ்சள்	சிவப்பு	நீலம்
பச்சை	நீலம்	சிவப்பு	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	நீலம்	சிவப்பு	நீலம்
சிவப்பு	பச்சை	மஞ்சள்	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	சிவப்பு	பச்சை	மஞ்சள்	பச்சை
நீலம்	மஞ்சள்	சிவப்பு	நீலம்	பச்சை	பச்சை	சிவப்பு	மஞ்சள்	மஞ்சள்	நீலம்	பச்சை
சிவப்பு	மஞ்சள்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்	பச்சை	நீலம்	சிவப்பு	மஞ்சள்	மஞ்சள்
மஞ்சள்	நீலம்	மஞ்சள்	நீலம்	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	பச்சை
பச்சை	மஞ்சள்	சிவப்பு	மஞ்சள்	நீலம்	மஞ்சள்	பச்சை	நீலம்	சிவப்பு	நீலம்	மஞ்சள்
சிவப்பு	பச்சை	நீலம்	சிவப்பு	மஞ்சள்	பச்சை	நீலம்	சிவப்பு	நீலம்	மஞ்சள்	சிவப்பு
நீலம்	மஞ்சள்	பச்சை	நீலம்	பச்சை	பச்சை	சிவப்பு	நீலம்	மஞ்சள்	பச்சை	பச்சை
மஞ்சள்	நீலம்	சிவப்பு	நீலம்	பச்சை	சிவப்பு	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	மஞ்சள்
சிவப்பு	நீலம்	மஞ்சள்	பச்சை	மஞ்சள்	சிவப்பு	பச்சை	மஞ்சள்	மஞ்சள்	நீலம்	பச்சை
மஞ்சள்	பச்சை	நீலம்	மஞ்சள்	சிவப்பு	மஞ்சள்	நீலம்	பச்சை	மஞ்சள்	சிவப்பு	நீலம்
நீலம்	மஞ்சள்	பச்சை	சிவப்பு	பச்சை	நீலம்	மஞ்சள்	பச்சை	சிவப்பு	நீலம்	சிவப்பு

Master chart

CONTROLS

S.NO.	AGE	SEX	OCCUPATION	EDUCAT	smoking	duration	BMI	FEV1	FVC	FEV1%	FEV1/FVC	SpO2% oximetry	MMSE	STROOP in sec	N1in ms latency	P300 ms latency	p300-N2µv amplitude
1	47	M	LABOURER	SCHOOL	NIL		24.539	2.9	3.45	104	0.84	100	30	60	98.8	281.3	8.58
2	40	M	LABOURER	SCHOOL	NIL		25.631	2.98	4	94	0.74	98	30	60	87.9	299	5.81
3	45	M	LABOURER	SCHOOL	present	OCCATIONAL	21.368	2.71	3.25	102	0.83	100	30	90	83.5	286.6	7.88
4	40	M	LAB TECH	COLLEGE	NIL		23.951	2.67	3.89	82	0.68	100	30	60	90.2	309.4	5.04
5	40	M	LABOURER	SCHOOL	present	OCCATIONAL	22.277	3	3.29	111	0.91	100	28	60	90.4	309.4	10.71
6	46	M	LABOURER	SCHOOL	present	15/D-1YR	23.335	2.23	4.12	68	0.54	98	30	60	100.9	287.5	6.55
7	40	M	COOLY	SCHOOL	present	OCCATIONAL	22.277	2.68	4.89	68	0.54	98	30	60	75	313.5	4.45
8	46	M	COMPUTER OPER	SCHOOL	present	OCCATIONAL	25.391	3.07	4.26	91	0.72	100	30	60	71.9	287.5	9.23
9	41	M	ELECTRICIAN	COLLEGE	present	OCCATIONAL	23.781	2.89	4.12	90	0.7	100	30	90	86.5	295.8	10.3
10	55	M	OFFICE ASST	SCHOOL	present	OCCATIONAL	23.781	2.79	4.27	79	0.65	100	29	60	76	310.4	5.48
11	55	M	CARPENTER	SCHOOL	present	10/D-20yrs	26.635	2.57	4.89	65	0.52	100	30	60	94.6	302.1	10.31
12	50	M	PLUMBER	SCHOOL	present	OCCATIONAL	24.221	2.67	3.98	81	0.67	98	29	60	76	310.4	5.48
13	56	M	CLERK	SCHOOL	4YRS		25.631	2.54	3.67	83	0.69	100	30	60	91.5	281	10.58
14	39	M	DRIVER	SCHOOL	present	OCCATIONAL	2.422	2.78	4.12	81	0.67	100	30	60	87.5	318.8	12.99
15	31	M	CLERK	SCHOOL	NIL		23.438	2.65	3.9	81	0.67	100	30	150	99.8	284.4	10.73
16	51	M	ELECTRICIAN	SCHOOL	present	OCCATIONAL	16.437	2.87	3.79	95	0.75	98	26	15	78.1	308.3	9.55
17	54	M	OFFICE ASST	SCHOOL	3YRS		26.898	2.67	4.1	79	0.65	99	29	90	62.5	296.9	10.68
18	58	M	LABOURER	SCHOOL	present	5/D-25yrs	23.733	2.96	4	95	0.75	99	30	90	89.6	288.5	10.8
19	59	M	LABOURER	SCHOOL	NIL		22.862	2.87	3.45	102	0.83	100	30	15	81.3	307.3	6.55
20	45	M	CONTRACTOR	SCHOOL	NIL		25.631	3.04	4	96	0.76	100	29	60	88.5	317.7	9.67
21	47	M	LABOURER	SCHOOL	NIL		22.583	2.67	3.25	101	0.82	99	28	60	89.6	302.1	8.05
22	54	M	LABOURER	SCHOOL	NIL		22.862	2.56	3.89	79	0.65	100	27	120	89.6	300	8.98
23	57	M	LABOURER	SCHOOL	NIL		23.438	2.83	3.29	105	0.86	99	30	120	78.1	310	6.54
24	57	M	LABOURER	SCHOOL	NIL		22.862	2.94	4.12	90	0.71	99	30	70	86.5	295.8	10.55
25	57	M	LABOURER	SCHOOL	NIL		23.011	2.91	4.23	88	0.68	100	29	60	85.5	299	6.9
26	58	M	ELECTRICIAN	SCHOOL	NIL		23.875	2.98	4.26	83	0.69	99	30	60	89.4	294	7.89
27	44	M	LABOURER	SCHOOL	NIL		26.563	3.11	4.86	76	0.63	99	30	60	76	312.4	5.81
28	60	M	LABOURER	SCHOOL	NIL		24.974	2.45	4.89	65	0.5	99	30	90	77.7	298.9	11.8
29	54	M	LABOURER	SCHOOL	NIL		23.875	2.98	4.89	84	0.6	98	29	60	87.5	298	10.89
30	50	M	LABOURER	SCHOOL	NIL		23.624	2.9	3.98	92	0.72	100	30	60	86.7	298.9	3.98
31	40	M	LABOURER	SCHOOL	NIL		26.835	2.89	3.67	98	0.78	100	30	60	83.3	293.6	5.43
32	56	M	LABOURER	SCHOOL	NIL		20.313	2.31	4.12	70	0.56	100	29	60	99.8	312.9	3.26
33	55	M	OFFICE ASST	SCHOOL	present	2/D-25yrs	21.484	2.78	3.9	90	0.71	100	29	60	78.9	311.8	8.13
34	49	M	OFFICE ASST	SCHOOL	NIL		20.313	2.31	3.79	74	0.6	100	30	60	83.9	298.9	8.34
35	47	M	OFFICE ASST	SCHOOL	NIL		18.424	2.91	4.1	89	0.7	100	30	60	79.9	304	9.87
36	47	M	PEON	SCHOOL	present	5/D-30yrs	18.424	2.82	4	89	0.7	100	30	60	87.6	309	8.98
37	47	M	OFFICE ASST	SCHOOL	present	OCCATIONAL	17.993	2.86	3.45	101	0.82	100	29	60	91.5	300.7	5.65
38	42	M	PEON	SCHOOL	present	10/DAY-30yrs	20.984	2.78	4	89	0.69	100	30	150	78.8	289.9	98.7
39	54	M	OFFICE ASST	SCHOOL	present	OCCATIONAL	20.761	2.45	3.25	95	0.75	100	30	120	76.4	287	8.98
40	40	M	OFFICE ASST	SCHOOL	present	OCCATIONAL	22.598	2.96	3.89	96	0.76	100	30	120	89.6	299.9	5.4
41	38	M	CAMERAMAN	COLLEGE	present	OCCATIONAL	21.774	2.95	3.29	108	0.89	100	30	120	89.7	300	7.98
42	50	M	OFFICE ASST	SCHOOL	present	4/D-20yrs	20.322	2.91	4.12	90	0.7	100	30	60	78.9	300.9	8.56
43	51	M	LABOURER	SCHOOL	present	OCCATIONAL	23.951	2.95	4.89	84	0.6	100	30	15sec	89.8	301.9	8.9
44	53	M	LAB ASST	SCHOOL	NIL		27.414	2.99	4.26	99	0.8	100	30	60	92.6	299	6.98
45	41	M	SUPERVISER	SCHOOL	NIL		25.1	3	4.86	85	0.61	100	30	120	74.9	307	4.31
46	56	M	LABOURER	SCHOOL	present	OCCATIONAL	16.135	3	0.6	77	0.64	100	29	60	89.6	299.9	5.4
47	60	M	LABOURER	SCHOOL	present	10/d-40yrs	16.135	2.98	4.89	74	0.6	100	30	30sec	81.3	309	8.89
48	58	M	LABOURER	SCHOOL	present	10/d-40yrs	23.922	3	3.98	96	0.75	100	30	60	89.8	300	9.67
49	55	M	LABOURER	SCHOOL	present	5/D-30yrs	23.922	2.78	3.67	96	0.75	100	30	30SEC	76.9	309.8	10.45
50	58	M	LABOURER	SCHOOL	present	10/D-10yrs	23.43	3	4.12	91	0.72	100	30	30SEC	79.8	310.8	7.58

COPD PATIENTS

S. No	AGEyrs	SEX	OCCUPATION	EDUCATION	duration	SMOKING	BMI		SPIROMETRY			oximetry	MMSE	STROOP	N1in ms	P300 in ms	p300-N2μv	ABG	
			NATURE	primary	illness-yrs	pack yrs		FEV1 P	FEV1	FVC	FEV1/FVC	SO2	score	in sec	latency	latency	amplitude	Po2	SO2
1	45	M	FISHERMEN	SCHOOL	5	12	25.299	76	1.02	1.63	0.62	98	28	150	106.6	345	4.25	66.1	94
2	65	M	Rtd govt s	SCHOOL	8	23	17.567	80	1.12	1.68	0.66	95	25	150	89.6	342.7	5.43	51.1	95
3	50	M	LABOURER	SCHOOL	6	45	20.395	81	1.33	1.98	0.67	95	23	150	100	356.9	5.81	83.5	93
4	50	M	ELECTRICIAN	SCHOOL	8	33	21.403	72	1.12	1.92	0.58	95	24	120	96.9	324.8	5.31	84.4	96
5	45	M	ELECTRICIAN	SCHOOL	10	12	20.957	85	1.41	2.02	0.69	96	27	90	99.8	324	4.85	98.2	95.5
6	55	M	LABOURER	SCHOOL	7	25	29.297	61	0.84	1.75	0.48	96	21	90	98.9	341.9	7.98	42.1	94
7	55	M	LABOURER	SCHOOL	4	35	18.262	48	0.44	1.15	0.39	95	26	90	97.9	302.1	3.31	89.2	96
8	55	M	LABOURER	SCHOOL	8	35	18.832	76	1.02	1.6	0.63	97	26	120	89.8	365.6	7.89	87	94
9	55	M	LABOURER	SCHOOL	11	35	19.052	95	0.5	0.65	0.75	94	26	120	85.4	330.2	5.98	90	93
10	48	M	LABOURER	SCHOOL	15	12	23.438	97	0.51	0.65	0.78	95	24	200	97	345.7	3.09	86	94
11	44	M	SELLER	SCHOOL	10	30	23.373	61	0.72	1.45	0.49	93	25	200	100.5	329	7.98	89	94
12	48	M	LABOURER	SCHOOL	13	12	18.195	81	1.01	1.5	0.67	94	24	200	117.2	359.8	5.74	91.8	84.3
13	42	M	ELECTRICIAN	SCHOOL	10	34	21.644	81	1.2	1.78	0.67	86	24	90	109.8	328.4	5.87	72.8	94
14	63	M	LABOURER	SCHOOL	8	23	17.578	85	1.45	2.02	0.71	95	24	90	96.9	382	5.31	92	90
15	52	M	LABOURER	SCHOOL	6	12	23.438	83	1.38	2	0.69	91	25	90	193.8	352.2	3.38	98.8	93
16	63	M	LABOURER	SCHOOL	7	45	18.73	83	1.4	2.01	0.69	94	27	120	139.6	354.8	4.05	56.8	92
17	48	M	AUTO DRIVER	SCHOOL	15	35	20.812	70	1.12	1.98	0.56	93	29	100	99.5	358.3	3.28	43.7	98.6
18	50	M	OFFICE ASST	SCHOOL	12	35	20.546	48	0.44	1.15	0.39	99	21	90	144.8	342.8	3.83	80.6	95
19	52	M	WATCHMAN	SCHOOL	13	25	24.221	95	2.05	2.71	0.75	98	30	90	110.4	331.4	3.9	56.3	96
20	66	M	LABOURER	SCHOOL	12	29	19.031	96	1.09	1.41	0.77	97	26	90	111.7	304.2	3.52	88.7	97
21	53	M	LOADMAN	SCHOOL	12	25	21.484	70	1.25	2.16	0.57	99	24	160	82.3	308.3	5.66	67.2	97
22	62	M	SHOP	SCHOOL	10	30	21.224	61	0.53	1.08	0.49	98	26	90	80.9	319.7	3.95	90	95
23	60	M	COOLY	SCHOOL	8	35	23.03	77	1.77	2.79	0.63	96	23	90	113	322.9	3.64	91.8	96
24	54	M	LABOURER	SCHOOL	9	40	20.812	60	1.05	2.18	0.48	96	26	240	87.9	324.8	7.89	66.6	95
25	58	M	LABOURER	SCHOOL	7	25	21.63	62	0.73	1.46	0.5	95	21	90	87.9	351.7	3.78	67.4	98
26	58	M	LABOURER	SCHOOL	6	20	23.011	65	1.38	2.59	0.53	98	26	200	89.6	305.2	5.9	91.8	96
27	45	M	LABOURER	SCHOOL	6	15	24.974	61	1.33	2.6	0.51	98	25	90	82.3	342.2	6.08	69.2	96
28	50	M	GOVT.PEON	SCHOOL	5	15	14.872	71	0.75	1.28	0.58	96	25	120	84.4	321.8	4.35	62.3	94
29	55	M	LABOURER	SCHOOL	7	13	24.238	60	0.69	1.39	0.49	94	23	120	89.6	302.1	5.87	62.5	95
30	54	M	LABOURER	SCHOOL	8	10	17.578	68	0.64	1.13	0.56	95	25	90	78.2	311.5	3.33	84.5	99
31	47	M	LABOURER	SCHOOL	9	35	23.438	75	0.85	1.38	0.61	100	25	120	98.5	384.4	7.02	89.1	90
32	55	M	LORRY SHED	SCHOOL	11	13	19.531	94	1.17	1.59	0.75	99	30	60	81.3	382.9	6.87	82	98
33	50	M	WATCHMAN	SCHOOL	15	40	30.458	74	0.85	1.4	0.6	98	25	90	87.5	306.3	5.87	82.8	96
34	52	M	LORRY SHED	SCHOOL	17	45	18.365	60	1.05	2.18	0.48	98	26	90	89.6	319.8	3.68	92.6	96
35	42	M	TAILOR	SCHOOL	13	35	22.039	83	1.52	2.2	0.69	97	25	90	99.5	305.2	4.31	90.5	96
36	60	M	LABOURER	SCHOOL	11	10	24.167	67	0.31	0.56	0.55	96	26	60	88.8	340.6	4.86	87.7	99
37	55	M	DECORATION	SCHOOL	7	10	17.8	76	1.5	2.4	0.62	99	24	60	71.9	342.8	3.99	62.5	94
38	48	M	COOLY	SCHOOL	8	20	22.641	48	0.4	1.1	0.36	95	24	90	76	324.7	5.11	44.6	98
39	37	M	LORRY DRIVER	SCHOOL	9	25	20.202	48	0.44	1.15	0.39	98	26	120	94	354.7	3.57	94.9	99
40	60	M	SECURITY	SCHOOL	13	35	18.491	67	0.94	1.68	0.55	99	24	90	98.6	345.1	6.98	66.6	97
41	45	M	COOLY	SCHOOL	6	25	20.546	68	1.02	1.77	0.57	98	24	100	89.7	301	7.98	78.1	95
42	42	M	SILVER POLISH	SCHOOL	7	10	19.592	56	0.47	1.02	0.46	96	24	100	76.1	340.7	4.86	82	94
43	55	M	SECURITY	SCHOOL	6	15	20.269	71	0.68	1.16	0.58	97	24	100	89	327.7	5.89	82.5	96
44	48	M	LABOURER	SCHOOL	10	15	16.135	71	0.67	1.15	0.58	96	26	120	84	346	4.08	81	96
45	53	M	PAINTER	SCHOOL	12	10	17.8	91	1.45	1.95	0.74	94	24	120	90	345	4.86	62.5	92
46	48	M	COOLY	SCHOOL	6	12	19.382	75	0.7	1.18	0.59	96	25	130	76	335.7	4.77	60.5	94.9
47	55	M	LABOURER	SCHOOL	6	24	17.8	77	0.7	1.15	0.6	95	24	90	98.8	321.7	5.87	82.5	95.9
48	60	M	COOLY	SCHOOL	5	26	18.975	60	0.62	1.29	0.48	96	21	90	78.1	312.9	6.89	100	97.9
49	62	M	SECURITY	SCHOOL	8	25	17.8	85	1.11	1.56	0.71	97	24	90	79.2	361	3.11	66.6	93.7
50	45	M	LABOURER	SCHOOL	9	30	18.975	68	0.61	1.15	0.53	96	25	90	87	345	4.66	85.2	96.6